Linking Dental Services to Treatment Outcomes for Diabetes
A Rapid Response Review

Eric Davis[1], Courtney Luterbach[1], Anupama Reddy[1], Jared Brewer[1], Esther Avendano[2], Elise Digga[2], Shayesteh Jahanfar[3], Daniel Weiner[4], David Leader[5], Sandeep Prabhu[6], Nanguneri Nirmala*[1]

*Corresponding author

1. Vindhya Data Science, Morrisville, NC, USA
2. Consultant
3. Department of Public Health and Community Medicine, Tufts School of Medicine, Boston, MA, 02111, USA
4. Division of Nephrology, Department of Medicine, Tufts Medical Center, Boston, MA, USA
5. Tufts University School of Dental Medicine, Boston, MA, USA
6. Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

Table of Contents

Background:

In the past several years, there has been increasing appreciation for the interconnectedness of oral health and whole body wellness, highlighted by the US Surgeon General's report in 2000[1]. Many subsequent efforts have established a connection between oral diseases, especially periodontitis, and impacts on a variety of systemic diseases[1]. The goal of this report is to review evidence on the efficacy of dental care/treatment in improving outcomes for patients with Diabetes.

Diabetes mellitus (DM) characterized by high blood sugar levels (HbA1c > 6.5%) affects approximately 37 million adults in the United States[2] and 500 million globally[3,4]. Diabetes is a chronic metabolic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. It is also termed as the "silent epidemic" causing a range of other diseases and health complications, including lower limb amputations, blindness, chronic kidney disease, and cardiovascular diseases[5]. Type II diabetes mellitus is a highly prevalent metabolic disorder characterized by the loss of ability to adequately control blood glucose levels due to insulin resistance in body tissues and typically emerges in adulthood. This is in contrast to type I diabetes mellitus (formerly commonly known as juvenile diabetes), where an autoimmune response results in the destruction of insulin-secreting β cells in the pancreas, requiring life-long insulin therapy[6]. Combined, these diseases affect ~10% of adults with 90% of the cases being type II diabetes, resulting in a substantial global disease burden[2].

Diabetes was the eighth leading cause of death in the United States in 2021 when considering death certificates that listed diabetes as a direct cause, however the mortality rate tripled when considering diabetes as an underlying or contributing cause[2,7]. Indeed, it is this spectrum of comorbidities that constitute the majority of the health burden of diabetes and factors that exacerbate the hyperglycemic damage to the vasculature are critical intervention loci in the management of diabetes[3]. These inflammatory exacerbating factors are now thought to include atherosclerosis, obesity, hypertension, changes in the gut microbiota, and others[8]. A key question in this review is whether oral inflammatory disease may contribute to or exacerbate the pathology of diabetes mellitus, and to collect evidence on dental treatments influencing diabetes outcomes.

Chronic oral diseases (COD) are a range of conditions that affect the mouth, including dental caries, gingival infection, periodontal disease, and tooth loss[4]. They are among the most common chronic diseases in the United States and can have a significant impact on overall health. COD are significantly more common and more severe in diabetic patients[5], with particular associations having been identified between diabetes and gingivitis and periodontitis. In addition, there may be increased risk in diabetes patients of systemic opportunistic infections after dental procedures such as implants to replace lost teeth[6]. High glucose levels in saliva from uncontrolled diabetes can feed bacteria in the mouth, which can create plaque that causes tooth decay, and even tooth loss. Dry mouth, also known as xerostomia, can be caused by high blood sugar levels in people with diabetes. Dry mouth can also increase the risk of tooth decay. Patients with diabetes are three times as likely to have oral candidiasis relative to healthy subjects[7]. Periodontitis is estimated to impact up to 90% of all adults worldwide and encompasses a range of severities ranging from mild gingivitis to severe loss of connective tissue resulting in painful inflammation and tooth loss. The most severe manifestations of periodontal disease are estimated to impact 5-15% of adults globally with perhaps even greater

prevalence in the United States[8]. One of the key factors in the development of periodontitis is a subdued granulocytic response to bacterial challenge in the oral cavity, resulting in increased plaque formation and eventually gum disease[9]. Indeed, one of the major clinical effects of diabetes is immune suppression, especially in polymorphonuclear cells due to alterations in immunometabolism[10].

Increasing evidence suggests that COD has a more complex relationship with diabetes than was previously appreciated, with the two being locked into a feedback loop where increasing COD severity results in greater systemic inflammation, which reduces glycemic control[3]. People with diabetes have a 2–3-fold greater risk for periodontitis[11] compared to people without diabetes, but also a higher incidence of caries due to dry mouth. The progression and severity of periodontitis are also greater in people with poorly controlled diabetes. According to the American Academy of Periodontology, 50% of diabetics up to the age of 35 suffer from periodontal disease, a figure that rises to 80% at the age of 45–54 years, compared to 60% in the healthy population. A growing body of data indicates that oral inflammation has an impact on general diseases[12]. This results in diabetes patients with severe COD having a significantly increased risk of all-cause mortality, highlighting the impact of oral health on cardiovascular, immune, and renal function. Figure 1 is a proposed causal model representing the factors that demonstrate an interplay between diabetes and oral disease. The relationship between oral health treatment and diabetes management has long been investigated in several studies but the exact correlation between oral health management and diabetes has not been comprehensively addressed.

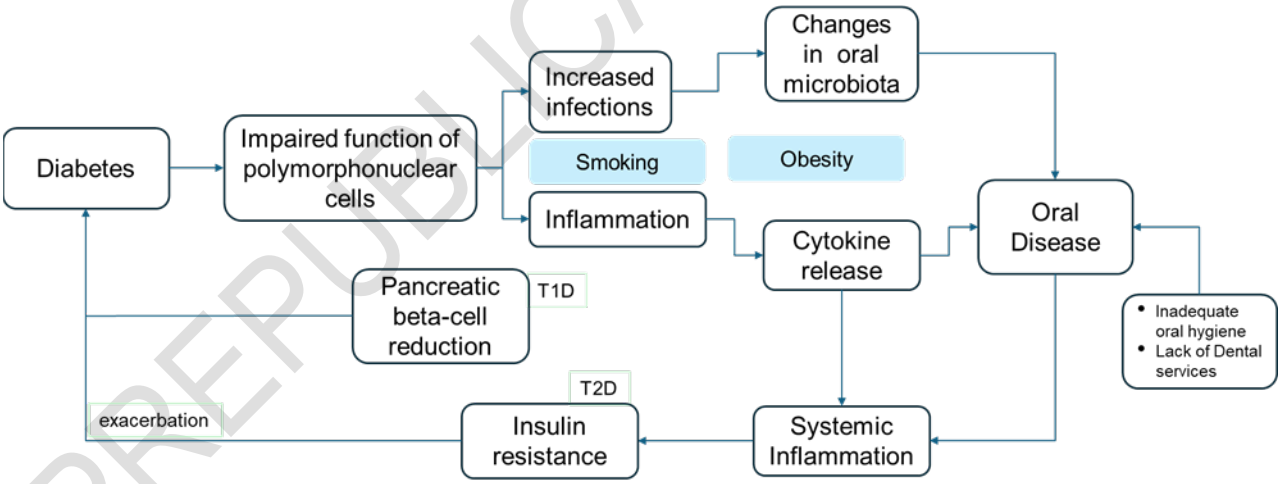


Figure 1. Schematic representation of a causal model depicting the relationship between DM and oral disease. Smoking and obesity are common risk factors for the two diseases. Single headed arrows represent the directionality of the specified outcome while double headed arrows signify the common causes and outcomes for both diseases.

In this rapid response, we seek to investigate potential relationships between oral health and Type 1 or Type 2 diabetes mellitus (T1DM, T2DM)) to address whether preventative oral healthcare and dental care interventions have an impact on DM outcomes. This review will be guided by three key questions (KQs) outlined below.

KQ1. What is the effectiveness of any non-periodontal dental services before or during particular treatments for persons with diabetes mellitus (type 1 and 2) on diabetic-related outcomes?
KQ2: What is the effectiveness of medically necessary periodontal services before or during particular treatments for persons with diabetes mellitus (type 1 and type 2) on diabetic-related outcomes?
KQ 3: Are there any dental services considered a standard of care for the management of persons with diabetes?

Methods:

This rapid review used the following methods as part of the process:

- Literature search and screening of the resulting articles
- Selection of studies for inclusion in this rapid response
- Data extraction for primary studies and systematic reviews
- Assembling of the evidence tables mapped to each key question
- Risk of bias (RoB) assessment for primary studies using the RoB 2[13], ROBINS[14] or NOS[15] tools
- AMSTAR2[16] quality assessment of systematic reviews
- Qualitative synthesis of the findings

Literature Search:

Using the framework shown in Table 1, searches of the literature were conducted of the following biomedical databases: OVID MEDLINE (PubMed interface) and practice guidelines. An experienced librarian conducted the searches. The search strategies used a combination of medical subject headings (i.e., controlled vocabularies) and keywords, and were written in the syntax of each database. The search strategies used terms for the intervention and condition as well as Boolean operators. All search results were limited to the English language and human species. Searches were initially restricted to the date range of May 2016 to May 2024 to ensure the literature was relevant to current trends. A detailed search strategy is included in Appendix A1. In addition to the articles regarding practice guidelines captured in the literature search, we also conducted a hand search to comprehensively capture the maximum number of articles relating to guidelines on this topic. We searched the websites of the following organizations: Centers for Disease Control and Prevention[17], American Diabetes Association[18] and, American Dental Association[19].

Table 1: PICOT table: Inclusion and exclusion criteria for studies in this rapid response

Study Parameter	**Inclusion Criteria**	**Exclusion Criteria**
Population	Non-pregnant adults >18 years with Type 1 or Type 2 Diabetes Mellitus (DM)	Persons with oral cancer
Intervention	Dental services before, during, or after treatment for DM:	Only Home dental care/oral hygiene as an intervention.

Study Parameter	Inclusion Criteria	Exclusion Criteria
	● Routine professional dental care (exam/cleaning) ● Periodontal treatment/cleaning ● Any dental treatment ● Patient education on oral health	
Comparator	No dental services for similar dental conditions in the intervention.	
Outcome(s)	**Primary Outcomes** ● HbA1c ● Fasting plasma glucose ● Systemic c-reactive protein or other inflammatory markers ● Incidence of adverse effects of diabetes treatment ● Infections (local and systemic, primary and secondary) ● Insulin resistance ● Rates of hospitalization **Secondary Outcomes** ● Lipid profile ● Cardiac Function ● Mortality ● Serious infection ● Quality of Life	Dental health outcomes and dental procedure outcomes are excluded.
Timing	Before, during or after treatment for DM. Follow-up time: minimum duration of 3 months.	None
Setting	US and additionally, Australia, Canada , Europe, Japan, Singapore. If the amount of evidence from studies in these countries is limited, other countries will be included.	Countries not listed in the inclusion list
Study Design	● Randomized controlled trials ● Systematic literature reviews (SLRs)/meta-analyses (MA) ● Controlled observational studies ● Practice Guidelines	● Non-controlled observational studies including case studies and case-series ● Scoping Reviews ● Laboratory studies ● Animal studies ● Non-clinical publications
Language	English language publications.	
Publication dates	May 2016 – May 2024 for RCTs and controlled observational studies	Articles published before 2016.

Study Parameter	Inclusion Criteria	Exclusion Criteria
	2020 - 2024 for reviews of reviews, systematic reviews and clinical practice guidelines	

We used Covidence[20] to manage the screening of the articles. 90% of the abstracts were reviewed by one reviewer, and the remaining 10% of the abstracts selected at random were reviewed by two members. Consensus was reached for any conflicts by discussion. At this stage, we excluded abstracts that did not describe a dental treatment, or those that had healthy controls in one arm. Screening of the full text was done in duplicate to ensure capture of as many articles as possible. Data extraction was done by one reviewer and verified by another.

Risk of Bias assessments:

For primary randomized controlled trials (RCTs), the Cochrane Risk of Bias (RoB) tool was used. Each RCT was classified as having low, moderate or high risk of bias. For single arm trials without a control group, the ROBINS tool was used to determine low, moderate, serious or critical risk of bias. Cohort studies were assessed using the Newcastle-Ottawa scale (NOS). Systematic reviews and umbrella reviews or reviews of reviews were assessed for quality using the AMSTAR2 tool to assess if the review was of high, moderate, low or critically low quality. To facilitate easier comprehension of the quality of the evidence across the different tools, we will employ the following terminology as shown in Table 2 below:

Table 2: Mapping of quality terms from the three tools assessing quality of the included studies.

Quality term used in this report	RoB Rating	ROBINS	NOS Rating	AMSTAR2 Rating
High	Low	Low	Good	High
Moderate	Some Concerns	Moderate	Fair	Moderate
Low	High	Serious	Poor	Low
Very low		Critical		Critically low

Data extraction:

Primary studies: data were extracted into tables for the following fields: first author, year, study design, type of DM, funding, study country, number of subjects, follow-up time, intervention, outcome category, outcome in intervention group, outcome in control group, statistical significance of the outcomes post-dental therapy, and RoB assessment. Data tables were generated for articles which were relevant evidence for each key question.

Review of reviews and systematic reviews: Data were extracted into tables for the following fields: first author, year, number of systematic reviews, type of DM, funding, study countries, period of study covered, intervention, main findings and strength of evidence.
Excluded studies: A list of excluded studies and reason for exclusion is provided in Appendix A2.

Results:

The literature search resulted in 601 records. After screening the abstracts, 89 articles were found eligible for full-text screening. Of these full-text articles, 27 articles were included that fulfilled the inclusion and exclusion criteria deemed relevant to the current review. A PRISMA flow diagram shown in Figure 2 summarizes the process of triaging the literature search results. Of the 27 articles that were included for data extraction, 16 articles were either randomized clinical trials or non-randomized controlled observational studies, 6 were SRs or meta-analyses, 3 were reviews of reviews and 2 were practice guidelines. In addition to the 2 articles that reported on practice guidelines in our search results, a hand search for guidelines identified additional 6 articles (Table 3). The primary studies were published in the time frame 2017 – 2024. All of the SRs were published in the time period 2017 – 2023. Some primary studies are also present in one or more of the SRs, because not all outcomes reported in the article were included in the SR/s where they were included. The list of 62 excluded articles and the reason for exclusion is given in Appendix A2. The list of all the primary studies in the URs and SRs is available in Appendix A3. Risk of Bias Assessments and the assessment of the quality of the SRs can be found in Appendix A4.

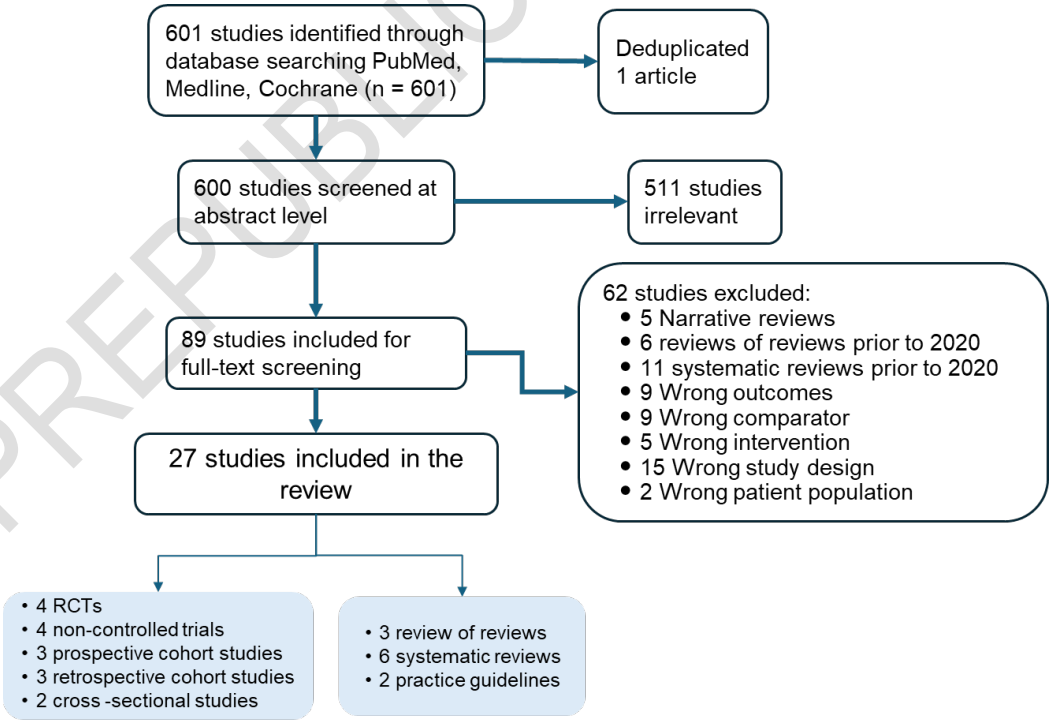


Figure 2: Flow diagram of literature search and triage process

Key Question 1:

What is the effectiveness of any non-periodontal dental services before or during particular treatments for persons with diabetes mellitus (type 1 and 2) on diabetic-related outcomes?

Key points:

The evidence regarding the impact of non-periodontal dental services on glycemic control and inflammatory markers in patients with diabetes is inconsistent. While some studies report improvements in glycemic control with non-periodontal dental services, the evidence is mixed, and the quality of the studies varies. The most methodologically sound study (retrospective cohort with a large sample size Zhang, 2023) found no significant change in HbA1c levels (HbA1c: -0.15, 95% CI: -0.42-0.13, moderate quality of evidence). A high level summary of the directionality of statistically significant outcomes in the studies mapping to KQ1 is in Table 1.1

Table 1.1: Statistically significant changes in outcomes in studies mapping to KQ1.

Study; Country; N; Intervention; Study Design; Follow-up time; Quality	**Glycemic Control**	**Inflammatory & Metabolic**	**Cardiac Function**	**Lipids**	**Infection, Comorbidities & Mortality**	**DM Disease activity/Quality of Life**
T2DM						
Pedroso[21] 2019; Brazil; 24; Gingivitis treatment; Single Arm study; 6 months, 12 months; High	ns: HbA1C ns: FPG	ns: CRP		ns: LDL ns: HDL ns: Tg ns: Tc		
Mizutani[22] 2024; Japan; 33; Dental prophylaxis without subgingival scaling; OHI; Single Arm study; 6 months; Moderate	↓ HbA1C ↓ FPG					
T1DM/T2DM						
Zhang[23] 2023; USA; 892;	ns: HbA1C					

Any preventative dental services; Retrospective Cohort study; 12 months; Moderate						
Enomoto[24] 2023; Japan; 1131; Dental treatment within last 2 months; Cross-sectional study; 2 months Low						↓ DM symptoms

Detailed description:

None of the URs or SRs identified in the literature search addressed KQ1. Table 1.2 below contains the descriptions of the characteristics of the included primary studies. The complete list of studies and descriptions of included study characteristics are in Table 1.3. This table provides detail the included primary studies addressing KQ1. Summarized are the details for each study regarding study location, funding source, DM stage, quality, study design, size of patient population, follow-up time, average baseline Hb1Ac level, dental services provided and key findings for DM-associated outcomes and their statistical significance. Outcomes for the latest two time points during follow-up are reported.

Primary Studies:

Pedroso (2019) in Brazil performed a high-quality single-arm study with 24 T2DM patients. Over a 12-month period, patients received gingivitis treatment, including supra-gingival scaling and prophylaxis with maintenance every 3 months. This study found no significant changes in HbA1c (-6.41 at 6 months, -3.85 at 12 months), FPG (-11.01 at 6 months, 0.29 at 12 months), or other inflammatory markers.

Mizutani (2024) from Japan conducted a moderate-quality single-arm study involving 33 T2DM patients over 6 months. Patients received dental prophylaxis without subgingival scaling along with oral hygiene instructions. This study observed significant improvements in glycemic control markers, with HbA1c decreasing by 22.92% and FPG by 10.7%.

Zhang (2023) conducted a retrospective cohort study in the USA, involving 892 subjects with Type 1 and Type 2 Diabetes Mellitus (T1DM and T2DM). This study, which is of moderate quality, found no significant change in HbA1c levels after preventative dental services (HbA1c: -0.15, 95% CI: -0.42-0.13).

Enomoto (2023) in Japan conducted a low-quality cross-sectional study with 1131 subjects with T1DM and T2DM. The study examined the effects of dental treatment over two months and found that continued dental treatment was associated with improved or stable diabetes

conditions. Only 5.6% of those who continued treatment experienced worsening diabetes symptoms, compared to 18.2% of those who discontinued treatment.

Table 1.2 Characteristics of studies mapping to KQ1.

Category	KQ1
Study Design	Non-randomized controlled observational (n=4)
Study Countries	Brazil, Japan, USA
DM type	T2DM: 2 studies, T1/T2DM: 2 studies
HbA1c across studies	Median values of 9.4, 9.6 (where reported[21,22])
Follow-up time	• T2DM: 6 – 12 months • T1/T2DM: 2 – 12 months
Interventions	• dental prophylaxis without subgingival scaling and with OHI (n=1) • supra-gingival scaling and prophylaxis (n=1), and • non-specific preventative dental services within a given time period (n=2)
Comparators	No dental follow-up or same patients at baseline prior to receiving treatment.
Outcomes (broad categories)	Glycemic control, inflammation, lipids, DM worsened within last 2 months

Outcomes Detail:

Glycemic Control:

Markers for glycemic control were measured in 3 of the 4 studies. Two studies[21,23] showed no improvement in glycemic control and 1 study[21] found a statistically significant reduction at follow-up (6 months). One study[21] was of high quality and two of the studies[22,23] were of moderate quality. The three studies differed in patient population and study design. Mizutani et al.[22] showed an improvement in both HbA1C and fasting plasma glucose ($P<0.05$) from baseline in individuals with T2DM receiving dental prophylaxis without subgingival scaling at 6 months follow-up. Zhang et al.[23] observed that use of preventive dental services was not significantly associated with HbA1c levels in individuals with diabetes (either T1DM or T2DM). Likewise, in individuals with T2DM and only gingivitis, Pedroso et al.[21] found no improvement of glycemic

control markers at 6- or 12-month follow-ups for those individuals receiving supra-gingival scaling and prophylaxis compared to pre-treatment measurements.

Inflammatory and Metabolic outcomes:

Pedroso et al.[21] found no significant change in CRP in patients with T2DM and gingivitis after receiving supra-gingival scaling and prophylaxis at either 6 or 12 months.

Cardiac Function:

Changes in cardiac function were not measured for this key question.

Lipids:

No significant change in lipid profiles were found in Pedroso et al.[21] for individuals with gingivitis receiving supra-gingival scaling and prophylaxis compared to pre-treatment values. Other studies did not evaluate these markers.

Infection, comorbidities, and mortality:

None of the 4 studies measured DM outcomes for this key question.

DM disease activity/Quality of Life:

Enomoto et al.[24] found a significant increase in self-reported exacerbation of DM symptoms in those individuals who discontinued dental treatment (non-specified) within the preceding 2 months.

Table 1.3: Primary studies mapping to KQ1.

Primary Studies with non-periodontal dental service [KQ1]							
Author, Year; Country; Funding Source; DM Stage; Quality	**Design; Total N; Time to Follow-up; Baseline HbA1c%**	**Dental Service**	**Outcome**	**Outcome in Dental Care Group**		**Outcome in Control Group**	**Statistically Significant findings of the outcomes post-dental therapy**
Pedroso[21], 2019; Brazil; None Reported; T2DM; High	Single-arm; 24; 6m, 12m; 9.4	*Gingivitis treatment:* supra-gingival scaling and prophylaxis; prophylaxis maintenance at 3m	% change relative to baseline; Patients with Gingivitis			No control group	No changes
				6 m	12 m		
			FPG	-11.01	0.29		
			HbA1c	-6.41	-3.85		
			CRP	47.62	0		
			Ox-LDL	3.33	-2.78		
			TC	-0.86	1.11		
			HDL-c	-3.55	-5.49		
			LDL-c	-1.77	8.08		
			TG	6.54	-7.63		
Mizutani, 2024[22]; Japan; Foundation; T2DM; Moderate	Single-arm; 33; 6 months; 9.6	Dental prophylaxis without subgingival scaling; OHI	*% change relative to baseline*			No control group	Glycemic control markers HbA1c and FPG were improved
			HbA1c	-22.92*			
			FPG	-10.7*			

Zhang, 2023[23]; USA; Foundation; T2DM, T1DM; Moderate	Retrospective Cohort study; 892; 1y; NR	Any preventative dental services	*Multivariable linear regression adjusted for sociodemographics, BMI, physical activity, medication, smoking, PD treatment, and comorbidities; Beta (95% CI)*			• Glycemic control unchanged.
			HbA1c	-0.15 (-0.42,0.13)		
Enomoto, 2023[24]; Japan; Foundation; T2DM, T1DM; Low	Cross-sectional study; 1131; 2 months; NR	Dental treatment within the last 2 months		*% Continued dental treatment*	*% Discontinued dental treatment*	• Improved or stable DM condition.
			DM worsened within last 2 months	58/1043 (5.6%)***	16/88 (18.2%)	

ns: not statistically significant; * p<0.05; ** p < 0.01; *** p < 0.001

Key Question 2:

What is the effectiveness of medically necessary periodontal services before or during particular treatments for persons with diabetes mellitus (type 1 and type 2) on diabetic-related outcomes?

Key points:

Summary: The evidence reported here is drawn from three reviews of reviews (URs – 2 high quality, one low quality), six systematic reviews (SRs, 2 high, 1 moderate and 3 low to very low quality) and twelve primary studies (4 RCTs and 8 observational studies – see table 2.1 for overall detail on the statistical significance of outcomes, study design and quality, and other study parameters). The RCTs, which are of high-quality evidence, generally support the effectiveness of periodontal therapy in improving glycemic control and reducing inflammatory markers in diabetic patients. Glycemic control also shows a consistent improvement in the URs and SRs overall. Observational studies, with varying levels of evidence quality (ranging from moderate to high), provide additional support for these benefits, particularly in managing long-term diabetic outcomes. However, the results can vary depending on the study design, population, and specific diabetic outcomes measured, indicating the need for careful consideration of the context and quality of evidence when interpreting these findings. There is insufficient evidence for outcomes relating to infection, comorbidities, mortality, and quality of life. Table 2.1 provides a high level view of the directionality and significance of outcomes in URs, SRs and primary studies mapping to KQ2.

Table 2.1: Statistically significant changes in outcomes in studies mapping to KQ2.

Author Year; Country; N; Intervention vs Control; Study Design; Quality	**Glycemic Control**	**Inflammatory & Metabolic**	**Cardiac Function**	**Lipids**	**Infection, Comorbidities & Mortality**
Author Year; # of SRs; # primary studies; Intervention vs Control; Quality Rating					
DiDomenico 2023[25]; 16; 73; NSPT vs none;	↓ HbA1C				

High					
Ata-Ali 2020[26]; 11; 27; NSPT and/or OHI and/or rinse and/or ABX vs none; High	↓ HbA1C				
Lavigne 2021[27]; 5 SRs, 3 URs; >42; NSPT vs none; Low	↓ HbA1C (weak evidence)				
Author Year; # of Studies; Total N; Intervention vs control; Quality	**Glycemic Control**	**Inflammatory & Metabolic**	**Cardiac Function**	**Lipids**	**Infection, Comorbidities & Mortality**
Wu 2023[28]; 17; 1448; NSPT or NSPT + ABX vs none/OHI/supragingival scaling; Moderate	↓ HbA1C				
EstevesLima 2021[29]; 18; 715; NSPT vs none; Very Low		↓ TNF-α			
Obadan-Udoh 2017[30]; 25; NSPT and/or surgery and/or OHI and/or ABX vs none; Very low	↓ HbA1C				
Simpson 2022[31]; 32; 3249; NSPT vs none or OHI; High	↓ HbA1C				
Elnour 2023[32]; 11; 1469; NSPT vs none; Very Low	↓ HbA1C				

Greggianin 2023[33]; 7; NR; NSPT vs none; Low	↓ HbA1C				
Author Year; Country; Total N; Intervention vs control; Quality	**Glycemic Control**	**Inflammatory & Metabolic**	**Cardiac Function**	**Lipids**	**Infection, Comorbidities & Mortality**
Pham 2022[34]; Vietnam; 42; NSPT + OHI vs OHI; RCT; High	↓ HbA1C ↓ FPG	↓ CRP			
Kolte 2023[35]; India; 60; NSPT + OHI vs oral prophylaxis with supragingival scaling + OHI; RCT; High	↓ HbA1C ↓ FPG ↓ PPG	↓ CRP ↓ TNF-α ↑ IL-10			
Wang 2020[36]; China; 55; NSPT+ OHI + tooth extraction if needed + plaque removal 2-3months post-treatment; RCT; High	ns: HbA1C	ns: IL-6 ns: CRP	↓ E/e' ratio ns: NT-proBNP		
Pedroso[21]; 2019; Brazil; 24; NSPT, OHI, prophylaxis maintenance at 3 months (no control group); Single Arm study; High	↓ HbA1C ↑ FPG	↓ CRP		ns: LDL ns: HDL ns: Tg ns: Tc	

Sundaram 2023[37]; India; 80; NSPT + OHI + plaque control (no control group); Randomized observational study; Moderate	↓ HbA1C ↓ FPG	↓ total protein ↓ albumin ↓ globulin			
Mammen 2017[38]; India; 40; NSPT + OHI + chlorhexidine + antimicrobial therapy vs none; Prospective cohort study; High	↓ HbA1c ↓ HOMA-2-IR ↓ HOMA 2-%S ↓ FPG	↓ C-peptide ↓ ESR ↓ WBC ns: albumin			
Bagde 2023[39]; India; 60; NSPT or NSPT + doxycycline vs none; Prospective cohort study; Low	↓ HbA1C				
Sato 2024[40]; Japan; 4279; NSPT + prophylaxis + support vs none; Prospective cohort study; High	↓ HbA1C				
Peng 2017[41]; Taiwan; 15195; NSPT and/or flap surgery vs other dental therapy; Retrospective cohort study; High					ns: stroke ↓ MI ↓ heart failure ns: CVD
Michalowicz 2023[42]; USA;	ns: HbA1C				↑ mortality ↓ hospitalizations

4879; NSPT vs cleaning vs none; Retrospective cohort study; High					
Saito 2017[43]; Japan; 9663; Periodontal treatment vs no treatment; Cross-sectional study; High	↓ HbA1C				
Milanesi 2023[44]; Brazil; 61; NSPT + OHI + maintenance up to 6 months vs none; RCT; High	ns: HbA1c ns: HOMA2-IR ns: HOMA2-B ns: HOMA2-%S ns: FPG	ns: CRP		ns: HDL ns: Tg	

ns: not statistically significant (p>0.05); ↓: statistically significant decrease in value at follow-up; ↑: statistically significant increase in value at follow-up; All changes shown are statistically significant (p<0.05). CRP: C-reactive protein; CVD: Cardiovascular disease; E/e' ratio: early diastolic mitral inflow velocity to early diastolic mitral annulus velocity; ESR: Erythrocyte sedimentation rate; FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c; HDL: High density lipoprotein; HOMA2-IR: Homeostatic Model Assessment for Insulin Resistance; HOMA2-B: Homeostatic Model Assessment for beta cell function; HOMA2-%S: Homeostatic Model Assessment for insulin sensitivity; MI: myocardial infarction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NSPT: non-surgical periodontal treatment; OHI: Oral hygiene instruction; TC: total cholesterol; Tg: Triglycerides; IL10: interleukin 10; IL6: interleukin 6; LDL: low density lipoprotein; QoL: Quality of Life; TNFα: tumor necrosis factor alpha; WBC: white blood cell count;

Detailed description:

The literature search resulted in the identification of three reviews of reviews[25–27] (URs) and six SRs and/or meta-analyses[28–33], and 12 primary studies.

Reviews of reviews (URs)

Two URs[25,26] were of high quality and one[27] was of moderate quality and covered the period 2005 – 2021. The URs contained 32 SRs and 3 URs overall. Glycemic control was the outcome reported in these URs. Two of the URs[25,26] of high quality concluded that NSPT is associated with improved glycemic control and the third UR[27] (low quality) also noted improvement in the glycemic index but concluded that there is weak evidence for this outcome due to the small

effect sizes. All the URs reported high heterogeneity and proposed that the main limitations for the heterogeneity in the results were most likely due to differences or inconsistencies in the definition of the severity of periodontal disease, or due to heterogeneity in baseline HbA1c levels. Details of the URs are given in Table 2.2.

Di Domenico et al . (2020): This UR used 16 SRs from which 27 studies were used for the meta-analysis for HbA1c, showing a significant improvement of 0.49% (95% CI [− 0.63, − 0.35], p < 0.001) at 3 months (high quality, more details in table) and at 6 months , although the HbA1c reduction relative to baseline at 6 months was lower than at 3 months.

Ata-Ali et al. (2020): Eleven SRs were included and for the meta-analysis, 11 studies were used . This was a high quality UR that also reported significant improvement in HbA1c of -0.32%(95%CI: [-0.50 to -0.15], p<0.001) with a concomitant reduction of fasting plasma glucose as well.

Lavigne and Forrest (2021): 5 SRs and 3 URs were used in this review (low quality). A separate meta-analysis was not performed. This UR also reported a reduction in HbA1c but effect sizes were small and/or not significant, and the component reviews had a high level of heterogeneity.

Systematic Reviews (SRs):

The six included SRs (one high and five low to very low quality – see Table 2.3) contained studies that measured outcomes up to 6 months. Key findings across SRs include improvements in glycemic control, as evidenced by statistically significant reductions in HbA1c levels[28,30–32] or HOMA-IR[33], the certainty of the evidence ranged from low to moderate with two SRs[28,32] not reporting these metrics. These two SRs showed high heterogeneity in the outcome. One SR[29] also found that NSPT significantly decreases serum TNF-α levels at six months in type 2 diabetes patients, and this SR was rated to be of very low quality. One SR[31] identified three studies that measured QoL outcomes showing limited evidence of a possible benefit from periodontal treatment. Each of these studies used a different questionnaire to measure QoL, hence the results could not be synthesized reliably. One SR was specifically of patients with diabetes above the age of 55 years[30]. In this SR as well, HbA1c levels decreased after 3 and 6 months post-NSPT.

Simpson et al. (2022): SR of high quality comprising 30 studies of both T1DM and T2DM reporting on HbA1c levels improving after periodontal treatment (3-month MD = -0.43, p < 0.00001 [30 studies]; 6-month MD = -0.30, p = 0.007 [11 studies]). The heterogeneity reported in this SR varied between 70-80%. The SR also included 3 studies reporting on quality of life (QoL) but the outcomes could not be combined in a meta-analysis since different questionnaires were used to collect the information to assess QoL.

Wu et al. (2023): SR comprising 17 studies (low quality) of patients with T2DM showed a reduction in HbA1c but the weighted mean difference of -0.024, (p = 0.003) was very small.

Elnour et al. (2023): SR comprising 11 studies (very low quality) of patients with T1DM and T2DM, also showed a very small effect size for HbA1c reduction post-NSPT.

Greggianin et al. (2023): SR comprising 7 studies (very low quality) of patients with T2DM reporting on HOMA-IR with a standardized mean difference of SMD = -0.35, p = 0.02.

EstevesLima et al (2021): SR comprising 18 studies (very low quality) reported on a significant reduction of TNF-α at 6 months post-NSPT.
Obadan-Udoh et al. (2017): SR of 22 studies (very low quality) including patients with T2DM and above the age of 55 years, and a qualitative synthesis showed that 14 of the studies reported HbA1c reductions. No meta-analysis was performed.

Table 2.2: Details of URs mapping to KQ2.

Study; Intervention; Quality of UR	# SRs;Years; # of primary studies included;	Quality rating of component SRs; Grade of Evidence	Main Findings	Heterogeneity - I^2	Main Limitations
DiDomenico 2023[25]; Periodontal therapy; High	16; 2010 - 2021; 27 out of 73 primary studies used for meta-analysis	AMSTAR2: 14 out rated very low, 1 low, 1 moderate quality; GRADE of evidence: not reported.	Improved glycemic control (HbA1c): • 3 months: −0.49% (95% CI [−0.63, − 0.35], p < 0.001), (18 studies) • 6 months: −0.38% (95% CI [−0.61, −0.16], p=0.0009)	3 months: 52% 6 months: 46%	• Differences in criteria adopted for the definition of periodontitis • Differences across therapeutic regimen of the patients
Ata-Ali 2020[30] ; Periodontal therapy; High	11 SRs; 2005 – 2014; 11 of 27 primary studies used for meta-analyses	AMSTAR2: High for all SRs. GRADE of Evidence: 6 SRs High, 4 Moderate and 1 Low.	Improved glycemic control: • HbA1c: -0.32%(95%CI: [-0.50, -0.15], p<0.001) • FPG: -11.59 mg/dl; 95%CI: -15.16, -8.01; p<0.001).	HbA1c: 83.2% FPG: 10.3%	• Heterogeneous definition of periodontal disease among the component SRs/studies.
Lavigne 2021[27]; Periodontal therapy; Low	5 SRs, 3 URs; 2007-2019; No separate meta-analysis	High overall for SRs. URs: Low, medium, medium-high; GRADE of Evidence: Not reported.	There is weak evidence that non-surgical NSPT improves glycemic control. Effect sizes were small.	NR	• Moderate to high heterogeneity reported in studies. • Likely due to inconsistency in defining periodontal disease. • Heterogeneity in baseline HbA1c levels.

CRP: C-reactive protein; FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c; NR: not reported; NSPT: non-surgical periodontal treatment; SR: systematic review; UR: review of reviews;

Table 2.3: SRs mapping to KQ2

Author Year; Quality of SR; Quality of included studies; Certainty of Evidence; Baseline HbA1c	**# of studies; # of patients; Diabetes type**	**Location**	**Treatment**	**Quality of included studies; Certainty of Evidence**	**Outcome**	**Results**	**I^2**
Simpson 2022[31]; High; Mostly Low; Moderate; **6.45 – 9.5**	30; 3249; T1DM, T2DM	Asia, Australia, Europe, South America, USA	NSPT	Mostly Low; Moderate	HbA1c (MD)	3-month = -0.43, 95%CI [-0.59, -0.28], p < 0.00001 [30 studies] 6-month = -0.30, 95%CI [-0.52, -0.08], p = 0.007 [11 studies]	3 months: 71% 6 months: 80%
	3				QoL	Evidence could not be synthesized reliably since the three studies used different questionnaires to assess QoL. Limited evidence of a possible benefit from periodontal treatment.	NR
Wu 2023[28]; Low; Moderate; NR; **6.0 – 9.5**	17; 1448; T2DM	Asia, Europe, South America, USA	NSPT or NSPT+ ABX	Moderate; NR	HbA1c (SMD)	NSPT: 3 month: -0.65, 95%CI [-0.97, -0.32]; p = 0.000; NSPT 6 month: −0.29%; 95% CI [−0.56, −0.02], p=0.033; NSPT+ABX: 3 month: -1.17%, 95%CI [-1.64, -0.71]; p=0.011;	66.30%
Elnour 2023[32]; Very Low; High; NR; **7.5 – 9.5%**	11; 1469; T2DM+T1DM	Asia, Australia, Europe, USA	NSPT	High; NR	HbA1c	3-12 month MD -0.24, 95%CI [-0.42, -0.06]; p=0.009	81%

Greggianin 2023[33]; Very Low; Mostly Low; Low; **5.6 – 8.0**	7 (2 RCT); NR; T2DM	Asia, Europe, USA	NSPT	Mostly Low; Low	HOMA-IR	SMD = -0.35, 95%CI [-0.63, -0.07], p = 0.02	0%
EstevesLima 2021[29]; Very Low; High; NR; **≥ 6.5**	18; 715; T2DM	Asia, Europe, South America, USA	NSPT	High; NR	TNFα (MD)	3-month: ns 6-month: -1.9, 95%CI [-3.05, -0.74], p = 0.001	3-month: 57% 6-month: 98%
Obadan-Udoh 2017[30]; Very Low; High; Very Low; **6.2 – 13.1%**	22; 1818; T2DM	Asia, Europe, South America, USA	NSPT+ OHI/ABX/photo dynamic therapy	High; Very Low	HbA1c	14/22 studies showed significant reductions; Average effect (range): -0.24% (+0.7 to -2.4)	High

ABX: antibiotics; CRP: C-reactive protein; CVD: Cardiovascular disease; E/e' ratio: early diastolic mitral inflow velocity to early diastolic mitral annulus velocity; ESR: Erythrocyte sedimentation rate; FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c; HOMA2-IR: Homeostatic Model Assessment for Insulin Resistance; MD: Mean difference; NSPT: non-surgical periodontal treatment; OHI: Oral hygiene instruction; SMD: standardized mean difference; QoL: Quality of Life; TNFa: tumor necrosis factor alpha;

Primary Studies:

Primary studies included for this key question evaluated the effectiveness of periodontal services for persons with T2DM and T1DM. Table 2.4 details the characteristics of the included primary studies mapping to KQ2. All of the studies were of patients with T2DM and one study also included patients with T1DM. Interventions were mainly non-surgical periodontal therapy (mainly NSPT) (11 studies) and two studies also included surgical intervention (flap surgery). More than half of the studies also included OHI (7 studies) and/or prophylaxis maintenance (7 studies). Comparators were no treatment, OHI, maintenance treatment (2 studies) or other unspecified treatment (1 study). Details of the primary studies and reported outcomes described below are given in Table 2.5. This table provides detail about the included primary studies addressing KQ2. Summarized are the details for each study regarding study location, funding source, DM stage, quality, study design, size of patient population, follow-up time, average baseline Hb1Ac level, dental services provided and key findings for DM-associated outcomes and their statistical significance.

Randomized Controlled Trials (RCTs):

Pham et al. (2022, Vietnam): Participants receiving scaling and root planning along with oral hygiene instruction showed significant reductions in HbA1c (-5.41%, high quality), fasting plasma glucose (FPG) (-6.06%, high quality), and C-reactive protein (CRP) (-13.04%, moderate quality) compared to the control group. These results suggest that periodontal therapy can significantly improve glycemic control and reduce inflammation in diabetic patients.

Milanesi et al. (2023, Brazil): No significant differences were observed in HbA1c, CRP, or FPG between the treated group (NSPT with OHI and regular maintenance) and the control group, indicating a lack of significant impact on diabetic outcomes from periodontal treatment in this study (high quality).

Kolte et al. (2023, India): The treatment group (NSPT with OHI) demonstrated significant reductions in HbA1c (-4.39%, high quality), TNF-α (-29.07%, high quality), CRP (-37.11%, high quality), and FPG (-17.33%, high quality) compared to the control group, indicating strong evidence that periodontal therapy can improve both glycemic control and inflammatory markers in diabetic patients.

Wang et al. (2020, China): The study observed no significant changes in glycemic variables (HbA1c and CRP), but improvements were noted in cardiovascular outcomes suggesting potential cardiovascular benefits of periodontal therapy (high quality).

Observational Studies:

Pedroso et al. (2019, Brazil): In this single-arm study, participants showed reductions in HbA1c (-7.45%, moderate quality) and CRP (-35.29%, moderate quality) at 6 months post-treatment, although FPG levels increased, indicating a mixed outcome with some positive effects on inflammation and glycemic control.

Sundaram et al. (2023, India): Both controlled and uncontrolled diabetic patients exhibited significant reductions in HbA1c (-16.48%, high quality), FPG (-24.12%, high quality), and several inflammatory markers post-periodontal treatment, suggesting periodontal therapy's efficacy in improving diabetic outcomes across different levels of glycemic control.

Mammen et al. (2017, India): This prospective cohort study found significant reductions in HbA1c (-2.48%, moderate quality) and improvements in insulin sensitivity (HOMA-IR) and inflammatory markers post-treatment, supporting the benefit of periodontal therapy on glycemic control and inflammation in diabetic patients.
Bagde et al. (2023, India): Significant reductions in HbA1c were observed in groups receiving NSPT with or without Doxycycline compared to the untreated group, suggesting that periodontal treatment can effectively lower HbA1c levels in diabetic patients (low quality).
Sato et al. (2024, Japan): The study demonstrated significant reductions in HbA1c among diabetic patients, particularly those with baseline HbA1c levels of 7.0-7.9% after periodontal treatment, indicating that such therapy can help manage blood sugar levels in this population (moderate quality).
Peng et al. (2017, Taiwan): This retrospective cohort study reported lower rates of myocardial infarction (MI) and heart failure among patients receiving periodontal therapy, with no significant impact on CVD or stroke incidence, suggesting cardiovascular benefits from periodontal treatment (high quality).
Michalowicz et al. (2023, USA): Periodontal treatment was associated with lower hospitalization risks and mixed results for mortality outcomes, indicating a potential but complex relationship between periodontal care and long-term diabetic health outcomes (high quality).
Saito et al. (2017, Japan): This cross-sectional study found small but significant reductions in HbA1c among older adults receiving periodontal treatment, reinforcing the potential benefits of periodontal care in managing diabetes in elderly populations (moderate quality).

Table 2.4: Characteristics of studies mapping to KQ2.

Category	**KQ2**
Study Design	Randomized Clinical Trial (RCT) (n=4)
	Randomized observational (n=1), single arm (n=1), cross-sectional (n=1); prospective cohort (n=3), retrospective cohort (n=2)
Study Countries	Brazil, Vietnam, India, China, Taiwan, USA, Japan
DM type	T2DM: 11 studies; T1DM/T2DM: 1 study
HbA1c across studies	6.1 – 9.4
Follow-up time	• T2DM: 1 month – 13.5 years • T1/T2DM: 3 – 6 months
Interventions	• NSPT only (n=1) • NSPT, prophylaxis (n=1) • NSPT, OHI, prophylaxis (n=2)

	• NSPT with only OHI (n=3) • NSPT, OHI, biweekly maintenance (n=1) • NSPT, OHI, chlorhexidine mouthwash, antibiotic therapy (n=1) • NSPT, antibiotic therapy (n=1), • NSPT, subgingival curettage and/or flap surgery (n=1), • NSPT and/or surgical procedures with or without maintenance (n=1), • non-specified non-surgical periodontal treatment (NSPT) with maintenance and flap surgery for severe periodontitis (PD) (n=1).
Comparators	• same persons at baseline prior to receiving NSPT (n=2) or • a control cohort of individuals or • receiving non-NSPT (i.e., no treatment [n=6] or • only OHI [n=2] or • oral prophylaxis with supragingival scaling with OHI [n=1] or • non-specific other treatment [n=1])
Outcomes (broad categories)	Glycemic control, lipids, inflammation, cardiovascular markers, mortality

NSPT: non-surgical periodontal treatment; OHI: oral hygiene instruction

Outcomes Detail:

Given below is a description of the outcomes reported in the studies included for KQ2.

Glycemic Control:

In most studies[21,28,30–40,42–44] (20/22), glycemic control was the primary outcome measured as the change in HbA1C or FPG. For primary studies in individuals with T2DM, HbA1c was significantly reduced at 3 or 6 months in 11 of the 12 studies measuring HbA1c. Four RCTs reported on this outcome. Wang et al.[36] reported in one RCT of no significant changes in glycemic control compared to a no treatment cohort at 6m follow-up. In contrast, Kolte et al[35] and Pham et al[9] observed in their RCTs, a significant improvement in glycemic control (HbA1c, FPG/PPG) in individuals treated with NSPT with OHI compared to those receiving oral prophylaxis with supragingival scaling and OHI. No significant changes in glycemic indices were observed in the RCT conducted by Milanesi et al[44]., in a population of individuals with either T1DM or T2DM compared to a no treatment cohort of a similar population of T1DM/T2DM.

Pedroso et al.[21] observed a significant improvement in glycemic control at 6 months but the reduction in HbA1c was not significant at 12 months. Studies by Saito et al.[43], and Sato et al.[40] also evaluated HbA1C levels at 1 year post-treatment. Sato et al. observed in those individuals with baseline HbA1c levels of 7.0%–7.9% who received periodontal therapy had statistically significantly better improvements in glycemic control than in individuals with no dental visits within the previous year. However, no significant change in glycemic control was observed for participants whose HbA1c levels were above 7.9 or between 6.5 - 6.9. Saito et al.[43] also found a significant decrease in HbA1c levels at 1 year following NSPT in individuals receiving 5 days or more of PD treatment throughout the previous year compared to controls.

No significant change in HbA1c was observed when NSPT was received fewer than 5 times during this time period.

The trends for other glycemic markers (*i.e.,* FPG, PPG, and HOMA 2) were consistent with HbA1c in trials when reported (n=6), except for Pedroso et al[21] where FPG levels were higher while HbA1c was reduced in individuals with T2DM receiving NSPT compared to pre-treatment values at 6m. Further discussion of these differences was not provided by the authors.

The addition of antimicrobial therapy with NSPT in individuals with T2DM was assessed in two studies (Mammen et al, Bagde et al.) compared to a no treatment control group. In a prospective cohort study of 60 patients[22], HbA1c levels were reduced significantly in individuals receiving NSPT (either NSPT or NSPT with antibiotic) compared to a no-treatment group. It is to be noted that there was no difference in HbA1c reductions between the two treated groups. Changes in HbA1c levels following NSPT were also assessed by SRs and URs as described above in a prior section.

Inflammatory and Metabolic markers:

CRP was measured in 5 trials in individuals with T2DM with three of the studies[14,15,18] showing a significant reduction at 6 months post-NSPT. Milanesi et al[44]., in an RCT, observed no significant change in CRP compared to a non-NPST control group in individuals with either T1DM or T2DM.

Inflammatory cytokine TNFα levels were lower after NSPT in individuals with T2DM in one primary study[35] and one SR. Likewise, the anti-inflammatory cytokine IL10 showed a significant increase after treatment of ~116%. Two studies measured serum albumin[17,21] and there was a significant decrease in albumin levels in one of the studies[17].

Cardiac Function:

Wang et al.[20] reported on the cardiac outcomes of NT-proBNP and E/e' ratio, both of which showed a statistically significant improvement at 6 months post-treatment compared to individuals with T2DM receiving only oral health instructions.

Lipids:

No significant changes were observed in lipid levels in the two studies with reported outcomes (T2DM and T1DM/T2DM populations)[14].

Infection, comorbidities, and mortality:

Limited data were available for these outcomes. Michalowicz et al., found that patients receiving a combination of both active with maintenance NSPT compared to a no treatment cohort were hospitalized 0.8 fewer times. However, active treatment alone was associated inversely with mortality in unadjusted models but after adjustments for variables relating to demographics, periodontitis severity and other co-morbidities, mortality was statistically significantly higher (odds ratio: 1.71) compared to the no treatment group. Mortality and infections were not assessed in other studies. Peng et al.[25], observed lower occurrence of myocardial infarction and heart failure in individuals with T2DM receiving NSPT compared to those receiving other dental

therapy. However, no differences in CVD or stroke incidence were observed in treated individuals in this study.

DM disease activity/Quality of Life:

These outcomes were not assessed for KQ2 in primary studies.

Table 2.5: Primary studies mapping to KQ2:

Author, Year; Country; Funding Source; DM Stage; Quality	**Design; Total N; Time to Follow-up; Age; Baseline HbA1c%**	**Dental Service**	**Outcome**	**Outcome in Dental Care Group**		**Outcome in Control Group**		**Statistically Significant findings of the outcomes post-dental therapy**
Randomized Clinical Trials								
Pham, 2022[34]; Vietnam; None Reported; T2DM; High	RCT; 42 (all smokers); data shown for 3m, 6m; 53.5 ± 8.0 years; **7.4 ± 0.4**	Treatment: NSPT with OHI Control: OHI		*change relative to baseline*				● Lowered FPG, HbA1c ● Lowered CRP
				3 m	6 m	3 m	6 m	
			FPG	-4.81**	-6.06***	1.31	2.18	
			HbA1c	-5.41**	-5.41***	1.37	4.11	
			CRP	-8.70	-13.04*	8.89	13.33	
Milanesi, 2023[44]; Brazil; Government, Academia; T2DM, T1DM; High	RCT; 61; 3m, 6m; <45 - >65 years **9.42±2.18**	Treatment: NSPT, OHI and biweekly maintenance appointments up to 3m and monthly appointments up to 6m	HbA1c	-6.48	-11.68	-6.39	-11.16	● No significant changes in HbA1c, CRP, HOMA indices or FPG in the treated group compared to the control group.
			CRP	-26.1	23.36	-14.16	-8.67	
			HOMA-2-IR	-11.42	-7.99	-6.69	8.55	
			HOMA 2-B	55.77	66	34.34	46.09	
			HOMA 2-%S	2.08	11.5	29.73	9.76	
			FPG	-19.96	-23.65	-12.71	-17.5	
			HDL-c	-2	3.11	3.43	0.35	

		Control: none	Tg	-49.89	-40.31	-1.87	10.49	
Kolte 2023[35]; India; None Reported; T2DM; High	RCT; 60; 6m; 30 – 60 years **6.83±0.46**	Treatment: NSPT + OHI at baseline, 3 and 6m Control: oral prophylaxis w/ supragingival scaling & OHI @ baseline, 3, 6m		*% change relative to baseline*				● TNF-α, CRP, HbA1c and both fasting and PPG levels were lower in treatment group compared to control at 6m ● IL-10 levels increased more in periodontal treatment group.
			IL-10	116.49***		11.24		
			TNF-α	-29.07***		-1.17		
			CRP	-37.11***		-2.50		
			FPG	-17.33***		-0.35		
			PPG	-20.64***		-0.11		
			HbA1c	-4.39***		-0.15		
Wang 2020[36]; China; Government, Academia; T2DM; High	RCT; 55; 6m; 64.4 ± 9.3 years **8.4 ± 1.1**	*Treatment*: OHI, NSPT. Tooth extraction if needed. OHI and plaque removal 2-3m post-treatment *Control*: OHI; reinforcement of OHI 2-3m after baseline		*% change relative to baseline*				● Improved LV diastolic function at 6m by a reduction in E/e' ratio ● No significant changes in glycemic variables
			HbA1c	1.19		1.20		
			CRP	-21.91		-1.29		
			IL-6	-22.04		4.94		
			NT-proBNP	-24.43		-0.68		
			E/e' ratio	-10.41*		6.78		
Observational Studies								
Pedroso, 2019[21]; Brazil; None Reported;	Single-arm; 24; 6m, 12m; 57.6±9.8 years;	OHI; NSPT; prophylaxis maintenance at 3m	% change relative to baseline			No control group		● Reduction in CRP at 12m and ● Increase in FPG at 6m
			Patients with Periodontitis					
				6 m	12 m			
			FPG	15.79*	6.59			
			HbA1c	-7.45*	-5.32			

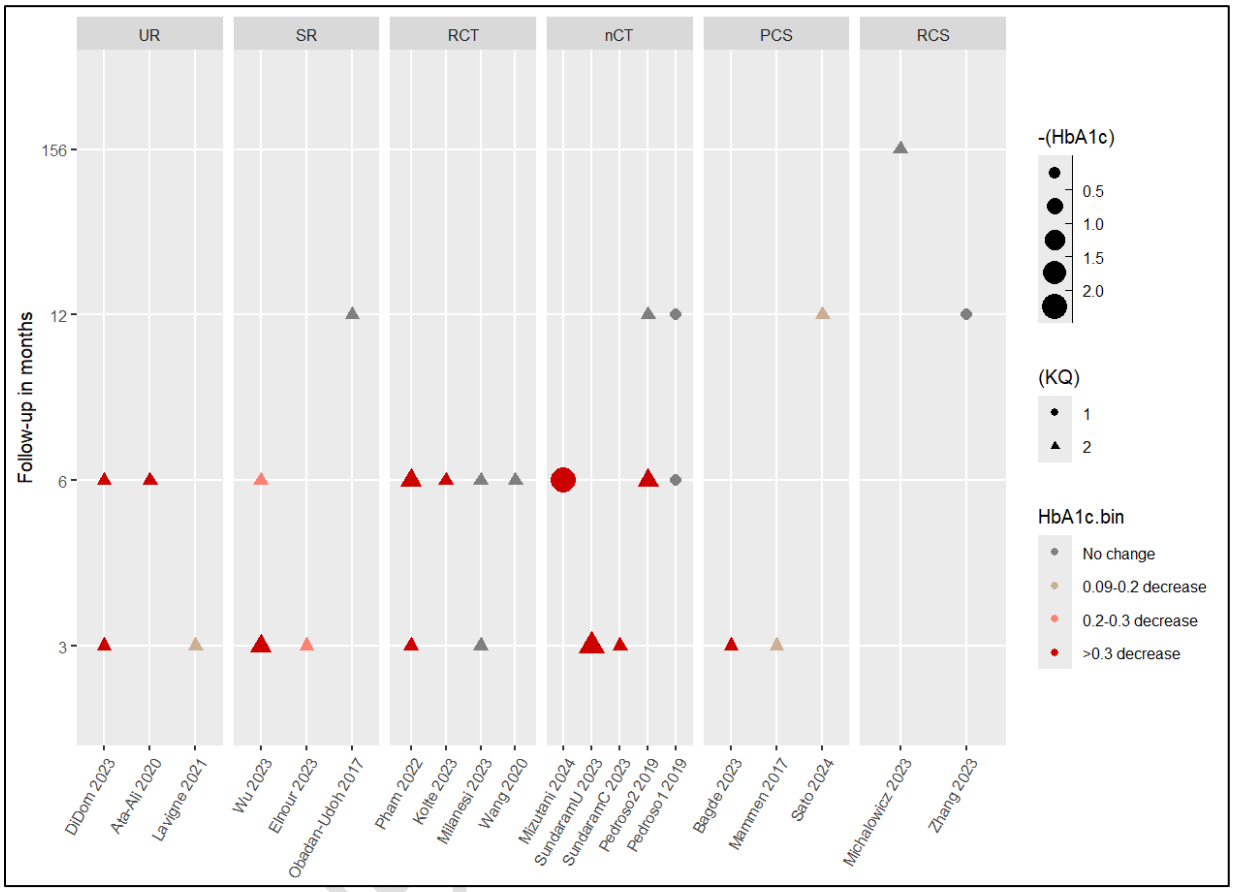
T2DM; High	**9.4**		CRP	-35.29*	-44.12		● Reduction in HbA1c levels at 6m
			Ox-LDL	1.81	2.41		
			TC	0.14	-1.14		
			HDL-c	-8.59	-11.09		
			LDL-c	2.87	8.89		
			TG	5.93	-13.86		
Sundaram 2023[37]; India; None Reported; T2DM; Moderate	Randomized observational study; 80; 3m; NR 6.1 (controlled DM), 9.1 (uncontrolled DM)	NSPT + OHI; plaque control instructional program twice a month for 3 months		*% change relative to baseline*			● Inflammatory markers, FPG and HbA1c were all reduced at 3m post-PD therapy in both controlled and uncontrolled T2DM individuals
				controlled DM	uncontrolled DM	No control group	
			FPG	-8.50***	-24.12***		
			HbA1c	-6.56***	-16.48***		
			Total Protein	-5.63***	-7.04***		
			Albumin	-9.52***	-7.32***		
			Globulin	-14.29***	-10.34***		
Mammen, 2017[38]; India; None Reported; T2DM; High	Prospective cohort study; 40; 3m; 30 – 60 years; **8.05 (range 7.52, 9.17)**	*Treatment:* NSPT, OHI, chlorhexidine mouthwash, antimicrobial therapy *Control group:* none		*% change relative to baseline*			● reduced HbA1c levels ● Reduced FPG levels ● Improved insulin sensitivity ● Lower insulin resistance
			C-peptide	-25.07***		95.40	
			HOMA-IR	-28.27***		91.93	
			HOMA 2- %S	40.12***		-39.23	
			Albumin	-0.50		1.30	
			ESR	-29.69***		-2.10	
			WBC	-4.79*		-0.41	
			HbA1c	-2.48*		0.58	
			FPG	-11.56*		5.17	
Bagde, 2023[39];	Prospective Cohort;	*Treatment: Group 2:* NSPT		*% change relative to baseline*			

India; None; T2DM; Low	60; 3m; 56.3 years; 8.4 (group 2), 8.5 (group 3)	*Group 3:* NSPT, Doxycycline *Group 1*: No PD treatment	HbA1c	Group 2	Group 1	● Reduction in HbA1c in both treated groups.
				-0.37*	1.15	
				Group 3	Group 1	
				-0.6***	1.15	
Sato, 2024[40]; Japan; Government; T2DM; High	Prospective cohort study; 4279; 1y; 56.8 (7.3) years; 6.5 - 8.0 (grouped by HbA1c ranges)	*Treatment:* prophylaxis, NSPT and ongoing support *Control*: No dental visit		*% change relative to baseline*		● Reduced HbA1c in those T2DM individuals with baseline HbA1c 7-7.9
			HbA1c: 6.5-6.9	3.03	3.00	
			HbA1c: 7.0-7.9	-0.35*	0.92	
			HbA1c: ≥ 8	-6.20	-6.08	
Peng, 2017[41]; Taiwan; None Reported; T2DM; High	Retrospective cohort study; 15195; 13y; 53.1±10.7yrs; **NR**	*Treatment*: Subgingival curettage, NSPT, and/or flap surgery *Control*: other dental therapy		*Hazard Ratio (95% CI) adjusted for age, gender, hypoglycemic agent, statin, antihypertensive drug, and comorbidities*		● Lower Rates of MI ● Lower rates of heart failure ● No difference in CVD and stroke incidence
			CVD	0.95 (0.90, 1.01)		
			MI	0.92 (0.85, 0.99)*		
			Stroke	0.95 (0.85, 1.06)		
			Heart failure	0.60 (0.45, 0.80)**		
Michalowicz, 2023[42]; USA;	Retrospective cohort study; 4879;	*Active Treatment*: Scaling or		*Odds Ratio (95% CI) compared to control and adjusted for multiple variables of demographics, PD disease & comorbidities*		● Lower risk of hospitalization. ● Unadjusted Active treatment

Government; T2DM; High	13.5y; 57.1 ± 13.2yrs; **6.9 – 7.5**	"deep cleaning" and/or surgical procedures *Maintenance:* cleaning *Control*: none	Hospitalization	Active Treatment: 1.08 (0.80, 1.46) Maintenance Only: 1.07 (0.92, 1.23) Active + Maintenance: 0.80 (0.64, 0.99)*	odds ratio (OR) was associated with decreased mortality; adjusted OR had statistically significantly higher mortality.
			CVD Hospitalization	0.83 (0.58, 1.18) 1.11 (0.89, 1.38) 0.73 (0.48, 1.09)	
			Mortality	1.71 (1.01, 2.92)* 0.82 (0.65, 1.04) 1.19 (0.77, 1.84)	
			CVD	1.35 (0.90, 2.02) 0.95 (0.79, 1.13) 0.94 (0.70, 1.26)	
			HbA1c	*Beta Estimates (95% CI)* 0.04 (-0.14, 0.21) 0.01 (-0.10, 0.11) -0.03 (-0.16, 0.10)	
Saito, 2017[43]; Japan; Foundation; T2DM; High	Cross-sectional study; 9663 (aged > 75 years); 1y; (aged > 75 years); 1y; **>6.5**	*Treatment:* NSPT (includes maintenance PD therapy) *Control:* No treatment		*Multivariate linear regression coefficient (95% CI) adjusted for age, sex, smoking habit, weight gain, BMI, physical activity and eating speed*	● Reduced HbA1c levels
			HbA1c (versus no treatment)	[PD] −0.035 (−0.063, −0.008)*	
			HbA1c (versus zero days of treatment)	[1-4 days] −0.031 (−0.065, 0.004) [≥5 days] −0.037 (−0.065, −0.009)*	

ns: not statistically significant; * p<0.05; ** p < 0.01; *** p < 0.001.

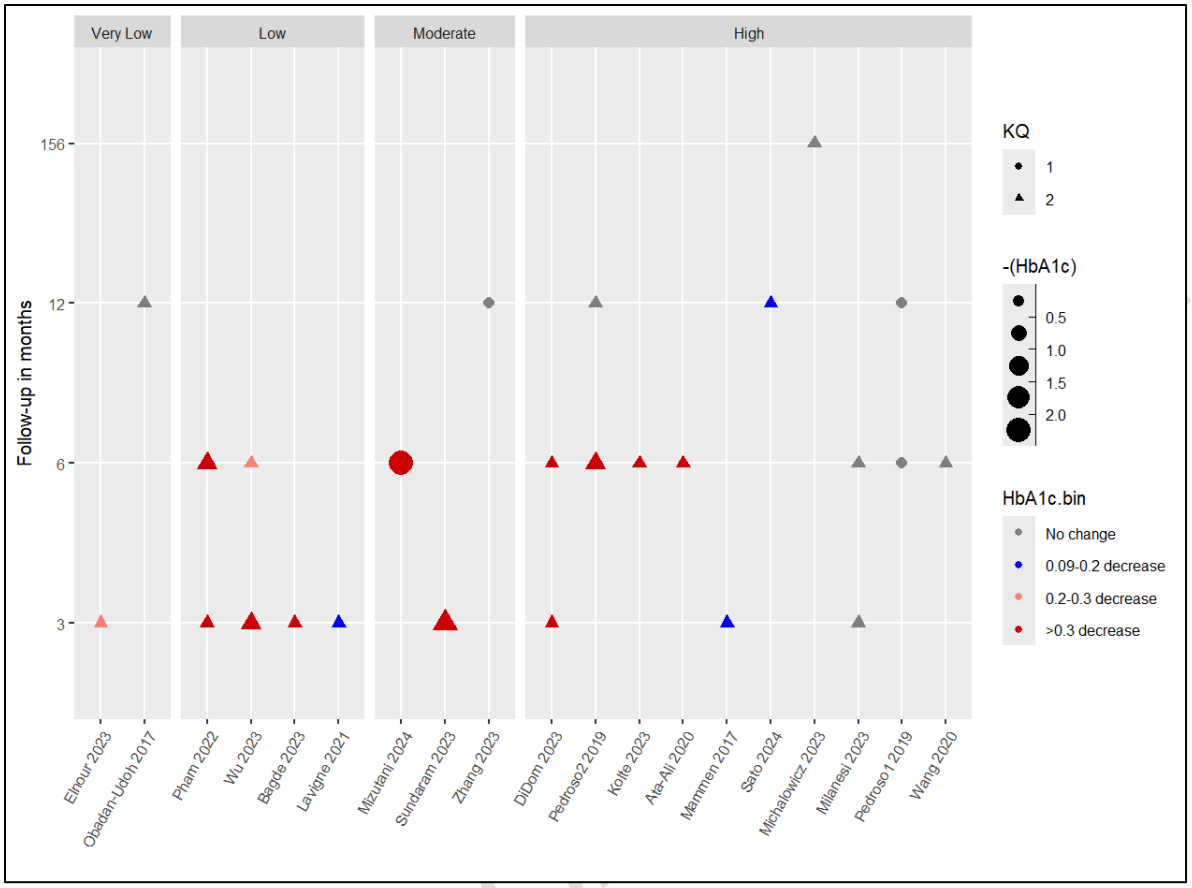
Overall most of the studies/meta-analyses show significant reductions in HbA1c and most of the reductions in HbA1c are better than 0.3%. In addition, most studies have a follow-up time of 3 months and/or 6 months. Most of the studies which have data for a follow-up time greater than 6 months do not show a change in HbA1c levels.



NA: not available; UR: Review of reviews; SR: systematic reviews; RCT: randomized clinical trial; nCT: non-controlled clinical trial; PCS: prospective cohort study; RCS: Retrospective cohort study

Figures 2.1: Improvement in HbA1c characterized by study type

Figure 2.2 shows the improvement in HbA1c levels characterized by study quality. Consistent reductions of HbA1c are seen in studies of low, medium and high quality studies, signifying a moderate level of evidence that periodontal treatment impacts reductions in HbA1c in patients with diabetes.



Figures 2.2: Improvement in HbA1c characterized by study quality

Key Question 3:

Are there any dental services considered a standard of care for the management of persons with diabetes?
To respond to this key question, we summarize below the results of our literature search and subsequent extract of key content from the included articles.

Practice Guidelines:

Our searches yielded 8 articles that contained recommendations for clinical practice guidelines for dental services for patients with diabetes. We summarize the overall recommendations made in Table 3.

The guidelines reflect the evidence base available in the literature showing the effectiveness of NSPT in improving glycemic control in people with diabetes. The guidelines in general tend to focus on periodontitis specifically with regard to oral health, mapping to KQ2. Most of the guidelines shown include recommendations for proactive treatment of periodontitis and advocate a close relationship between the PCP and the oral health professionals (KQ2). All guidelines[45–47] emphasize the importance of educating patients with diabetes about the link

between oral health and diabetes management (KQ1). Regular dental visits are recommended in the guidelines[45–47] (KQ1). The guidelines provide recommendations for patients, oral health professionals as well as the PCPs. Patients are advised to take measures to improve and maintain good oral health practices. Recommendations to the PCP are for them to advice and educate patients on the bidirectional relationship between periodontitis and diabetes and to monitor oral health regularly and obtain prompt treatment for any periodontal condition (KQ2). Good communication between the patients and the care providers has been reiterated in several of the guidelines.

Table 3: Guidelines for oral care for patients with T1DM or T2DM

Author Year	**Article Title**	**Type of article**	**Overall recommendations regarding dental care strategy**
Nice Guideline Development Team 2022[48]	NICE Guideline: Periodontal treatment to improve diabetic control in adults with type 1 or type 2 diabetes. Mainly used Simpson et al[48] SR to formulate recommendations.	Evidence review underpinning recommendations for dental care for patients with DM.	Type 1[48] and Type 2[49] DM caregivers to advise adults with T1DM/T2DM at their annual review that (recommendations 1.15.1 to 1.15.4 of Type 1 diabetes in adults: diagnosis and management guideline and recommendations 1.8.1 to 1.8.4 of the Type 2 diabetes in adults: management guideline): ● they are at higher risk of periodontitis ● managing periodontitis can improve their blood glucose control and can reduce their risk of hyperglycemia. ● it is recommended to have regular oral health reviews ● to offer dental appointments to manage and treat their periodontitis (at a frequency based on their oral health needs)
Adda 2021[49]	Consensus report of the joint workshop of the Italian Society of Diabetology, Italian Society of Periodontology and Implantology, Italian Association of Clinical PCPs	Guideline	**PCP**: ● To inform the diabetic patient about the high risk of periodontitis ● To ask the patient to be checked for the presence of signs and symptoms of periodontitis ● To refer the patient to the dentist for a thorough exam of the oral conditions; ● To inform the patient that good oral health may be beneficial for glycemic control; ● To advise the patient to carry out dental checkups at least once per year even in the absence of pain or other symptoms. **Dentist:** ● To inform the patient about the association between periodontitis and systemic diseases; ● To collect a detailed individual and familiar medical history and notice patient's BMI and to advise the

			patients to perform blood tests whenever recent blood analysis results are not available (>1 year); ● To advise for a diabetes checkup in patients with severe periodontitis and first degree familiarity for diabetes;
Herrera 2024[50]	Periodontal diseases and cardiovascular diseases, diabetes, and respiratory diseases: Summary of the consensus report by the European Federation of Periodontology and WONCA Europe.	Report	● Raise awareness amongst family doctors, general dentists, other healthcare professionals, patients, and health authorities of the importance of periodontitis to diabetes control and complications, the impact of hyperglycemia upon periodontitis, and compromised healing following periodontal therapy. ● Two-way communication between family doctors and OHPs is key to collaborative management, and should be documented in the patient's health record and be supported by written communication between teams. ● Potential role of PCPs in early detection/screening/prevention of periodontal diseases ● PCPs should advise oral health assessments and periodontal care to patients with diabetes or patients who are prediabetic.
Tangpricha 2023[51]	American Association of Clinical Endocrinology Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm – 2023 Update	Guideline	No recommendations for dental care.
American Diabetes Association 2023[18]	Standards of Care in Diabetes	Guideline	No recommendations for dental care.
Sanz 2017[45]	Scientific evidence on the links between periodontal diseases and diabetes: Consensus		● Periodontal evaluation should be part of diabetes care visits, and patients should be asked about signs and symptoms of periodontitis. ● Referral for a periodontal examination should occur for all people with newly diagnosed diabetes.

	report and guidelines of the joint workshop on periodontal diseases and diabetes by the International Diabetes Federation and the European Federation of Periodontology		● Oral health professionals should provide oral health education to all patients with diabetes and tailor oral hygiene regimes. ● NSPT should be provided to people with diabetes, as it may help improve glycemic control. ● People with diabetes should be advised to seek dental care regularly and report any signs of gum disease. ● Oral health professionals should evaluate patients with diabetes for other potential oral complications. ● Patients with diabetes who have extensive tooth loss should be encouraged to pursue dental rehabilitation. ● Patients with diabetes should inform their dentist about their diabetes control and changes in medications. ● Patients with diabetes should keep their mouth and whole body as healthy as possible with regular dental and medical care.
Lavigne 2021[27]	An umbrella review of SRs of the relationship between type 2 diabetes and periodontitis: Position paper from the Canadian Dental Hygienists Association	Position Paper. Quality of the UR: high (Amstar2 rating).	● Dental hygienists can play a pivotal role in reducing significant health care costs by screening their clients, identifying those who may potentially have diabetes unknowingly, providing NSPT to reduce the inflammatory load, and ensuring these clients receive the necessary education and health promotion information to potentially reduce the serious effects of these comorbidities.
Ahern 2021[46]	The integration of oral health-related best practice recommendations in the management of patients with diabetes: a cross-sectional survey of primary care physicians	Survey	● Survey results: ● 61% of PCPs were aware that periodontitis can have a negative impact on glycemic control ● 76% were aware that poor glycemic control can negatively impact periodontal health ● ~90% of PCPs surveyed tend not to inform their patients with diabetes of the bidirectional link with periodontitis, or provide advice or referral to attend dental care as part of diabetes management. ● 32% of PCPs felt confident facilitating access for their patients to dentists. However, 93% of PCPs do not refer patients with diabetes to dentists as part of a diabetes management plan.

Discussion:

Based on the outcomes from the summarized studies, clinicians should note that the evidence regarding the impact of preventive dental services (KQ1) on glycemic control in diabetic patients is inconsistent. The most robust study (Zhang, 2023) found no significant change in HbA1c levels after such interventions, suggesting clinicians should be cautious in expecting substantial glycemic benefits from preventive dental services alone. While gingivitis treatments, such as supra-gingival scaling and prophylaxis, have maintained periodontal health, they did not significantly improve glycemic or inflammatory markers in the high-quality study by Pedroso (2019). This implies that while essential for oral health, these treatments may not provide notable systemic benefits in terms of glycemic control.

The study by Mizutani (2024) indicates that dental prophylaxis without subgingival scaling can significantly improve glycemic control markers (HbA1c and FPG) in T2DM patients, suggesting that specific types of dental care could have systemic benefits. However, more high-quality research is needed to confirm these results. Additionally, the study by Enomoto (2023) highlights that continuous dental treatment is associated with improved or stable diabetes conditions while discontinuing dental treatment can lead to worsening diabetes symptoms. Therefore, it may be to patients' benefit to maintain regular dental care as part of their diabetes management plan.

The clinical implications of the studies reviewed as part of KQ2 are significant, particularly regarding managing diabetes mellitus through periodontal therapy. The randomized controlled trials reviewed provide strong evidence that periodontal treatment can improve glycemic control and inflammatory markers, which are critical in managing both type 1 and type 2 diabetes. The reduction in HbA1c levels observed in several high-quality RCTs is clinically significant, as even small reductions in HbA1c are associated with a decreased risk of diabetes-related complications, including cardiovascular diseases, neuropathy, and retinopathy. This suggests that integrating periodontal therapy into routine care for diabetic patients could be a beneficial strategy to improve overall disease management.

The observational studies, while offering additional support for the benefits of periodontal therapy, also highlight the importance of considering the heterogeneity in study design and population. The mixed results from these studies underscore the need for personalized treatment plans and further research to identify which subgroups of diabetic patients might benefit the most from periodontal interventions.

Clinical Implications

The findings from the reviewed URs, SRs and primary studies suggest that periodontal therapy has the potential to play a significant role in managing diabetes mellitus, particularly through the reduction of HbA1c levels and inflammatory markers. The reductions in HbA1c observed in high-quality RCTs are particularly clinically relevant, as even modest decreases in HbA1c are associated with a reduced risk of complications such as cardiovascular disease, neuropathy, and retinopathy. This underscores the importance of considering periodontal therapy as part of a comprehensive approach to diabetes management.

The observed decreases in inflammatory markers like CRP, TNF-α, and IL-6 further highlight the systemic benefits of periodontal therapy. By reducing systemic inflammation, periodontal

treatment may help mitigate some of the metabolic disturbances associated with diabetes, potentially leading to better overall disease control and fewer complications.
Moreover, the improvements in cardiovascular outcomes, such as the reduction in the E/e' ratio reported in one RCT, suggest that periodontal therapy might also offer cardiovascular benefits to diabetic patients, further enhancing its clinical value. Given the high burden of cardiovascular disease in diabetic populations, these findings, albeit in only a minority of studies, could justify the inclusion of periodontal therapy in routine diabetes care protocols.

Limitations

Despite the promising findings, there are several limitations to the current body of evidence. The variability in study designs, including differences in periodontal treatment protocols, follow-up durations, and outcome measures, complicates the ability to draw definitive conclusions about the long-term benefits of periodontal therapy. Additionally, while RCTs provide high-quality evidence, the observational studies included in the review generally offer lower quality evidence due to potential biases such as confounding factors and the lack of randomization.
Another limitation is the lack of standardization in the definition and measurement of key outcomes, such as HbA1c and inflammatory markers, across studies. This lack of consistency makes it difficult to compare results across different studies and populations.
Furthermore, many studies had relatively short follow-up periods, which may not fully capture the long-term effects of periodontal therapy on diabetic outcomes. Longer follow-up periods are necessary to determine whether the observed benefits are sustained over time and whether they translate into meaningful reductions in diabetes-related complications and mortality.
Lastly, the generalizability of the findings may be limited by the specific populations studied. While the inclusion of diverse populations from different countries is a strength, the results may not apply universally to all diabetic patients, particularly those with different baseline characteristics or comorbid conditions.

Strengths of the Studies: The strength of these studies lies in the consistent finding across multiple RCTs, observational studies as well as SRs and URs, that periodontal therapy can significantly lower HbA1c levels, a key indicator of long-term glycemic control. The inclusion of diverse populations from different countries also adds to the generalizability of the findings, suggesting that the benefits of periodontal therapy for diabetic outcomes may apply broadly across various demographic groups.

Future Research Directions: Future studies should focus on standardizing periodontal treatment protocols and outcome measures to facilitate more consistent comparisons across studies. Longitudinal studies with extended follow-up periods are also needed to assess the long-term impact of periodontal therapy on diabetic complications and overall survival. Studies should also include subgroup analyses based on baseline HbA1c levels, age, gender, obesity and smoking status of the patients, since these parameters are known risk factors in diabetes[52].
Additionally, research should explore the mechanisms underlying the observed improvements in glycemic control and inflammation to better understand how periodontal therapy interacts with the metabolic processes in diabetic patients.
Moreover, future research should aim to identify specific subgroups of diabetic patients who may derive the most benefit from periodontal therapy. For instance, exploring the role of baseline inflammation levels, the stage of diabetes, the severity of periodontitis and the

presence of other comorbid conditions could help tailor periodontal interventions to individual patient needs. This personalized approach could maximize the clinical benefits of periodontal therapy while minimizing the risks and costs associated with treatment.
Conclusion: The current literature supports the clinical importance of periodontal therapy as an adjunctive treatment for improving diabetic outcomes, particularly in reducing HbA1c levels and systemic inflammation. However, further high-quality research is needed to confirm these findings and optimize treatment strategies for different patient populations.

References

(1) U.S. Department of Health and Human Services. *Oral Health in America: A Report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human Services, National Institute of Dental and Craniofacial Research, National Institutes of Health, 2000.*; 2000.

(2) Cho, N. H.; Shaw, J. E.; Karuranga, S.; Huang, Y.; Da Rocha Fernandes, J. D.; Ohlrogge, A. W.; Malanda, B. IDF Diabetes Atlas: Global Estimates of Diabetes Prevalence for 2017 and Projections for 2045. *Diabetes Research and Clinical Practice* **2018**, *138*, 271–281. https://doi.org/10.1016/j.diabres.2018.02.023.

(3) Tsalamandris, S.; Antonopoulos, A. S.; Oikonomou, E.; Papamikroulis, G.-A.; Vogiatzi, G.; Papaioannou, S.; Deftereos, S.; Tousoulis, D. The Role of Inflammation in Diabetes: Current Concepts and Future Perspectives. *Eur Cardiol* **2019**, *14* (1), 50–59. https://doi.org/10.15420/ecr.2018.33.1.

(4) Heydari, M.-H.; Sharifi, F.; Sobhaninejad, S.; Sharifi, A.; Alizadeh, L.; Darmiani, S.; Bijari, S.; Parvaie, P.; Bakhshandeh, S.; Shoaee, S.; Khoshnevisan, M.-H. The Association between Dental Caries, Periodontal Diseases, and Tooth Loss with Diabetes Mellitus among the Elderly Population. *J Diabetes Metab Disord* **2024**, *23* (1), 1371–1380. https://doi.org/10.1007/s40200-024-01434-2.

(5) Triebl, Z.; Bencze, B.; Bányai, D.; Rózsa, N.; Hermann, P.; Végh, D. Poor Glycemic Control Impairs Oral Health in Children with Type 1 Diabetes Mellitus - a Systematic Review and Meta-Analysis. *BMC Oral Health* **2024**, *24* (1), 748. https://doi.org/10.1186/s12903-024-04516-y.

(6) Al Ansari, Y.; Shahwan, H.; Chrcanovic, B. R. Diabetes Mellitus and Dental Implants: A Systematic Review and Meta-Analysis. *Materials (Basel)* **2022**, *15* (9), 3227. https://doi.org/10.3390/ma15093227.

(7) Rodríguez-Archilla, A.; Piedra-Rosales, C. Candida Species Oral Detection and Infection in Patients with Diabetes Mellitus: A Meta-Analysis. **2021**. https://doi.org/10.5281/ZENODO.4495286.

(8) Germen, M.; Baser, U.; Lacin, C. C.; Fıratlı, E.; İşsever, H.; Yalcin, F. Periodontitis Prevalence, Severity, and Risk Factors: A Comparison of the AAP/CDC Case Definition and the EFP/AAP Classification. *Int J Environ Res Public Health* **2021**, *18* (7), 3459. https://doi.org/10.3390/ijerph18073459.

(9) Uriarte, S. M.; Hajishengallis, G. Neutrophils in the Periodontium: Interactions with Pathogens and Roles in Tissue Homeostasis and Inflammation. *Immunol Rev* **2023**, *314* (1), 93–110. https://doi.org/10.1111/imr.13152.

(10) Dowey, R.; Iqbal, A.; Heller, S. R.; Sabroe, I.; Prince, L. R. A Bittersweet Response to Infection in Diabetes; Targeting Neutrophils to Modify Inflammation and Improve Host Immunity. *Front. Immunol.* **2021**, *12*, 678771. https://doi.org/10.3389/fimmu.2021.678771.

(11) Löe, H. Periodontal Disease: The Sixth Complication of Diabetes Mellitus. *Diabetes Care* **1993**, *16* (1), 329–334. https://doi.org/10.2337/diacare.16.1.329.

(12) National Institutes of Health. *Oral Health Care in America: Advances and Challenges. Bethesda, MD: US Department of Health and Human Services, National Institutes of Health, National Institute of Dental and Craniofacial Research.*; 2021.

(13) Sterne, J. A. C.; Savović, J.; Page, M. J.; Elbers, R. G.; Blencowe, N. S.; Boutron, I.; Cates, C. J.; Cheng, H.-Y.; Corbett, M. S.; Eldridge, S. M.; Emberson, J. R.; Hernán, M. A.; Hopewell, S.; Hróbjartsson, A.; Junqueira, D. R.; Jüni, P.; Kirkham, J. J.; Lasserson, T.; Li, T.; McAleenan, A.; Reeves, B. C.; Shepperd, S.; Shrier, I.; Stewart, L. A.; Tilling, K.; White,

I. R.; Whiting, P. F.; Higgins, J. P. T. RoB 2: A Revised Tool for Assessing Risk of Bias in Randomised Trials. *BMJ* **2019**, l4898. https://doi.org/10.1136/bmj.l4898.
(14) Sterne, J. A.; Hernán, M. A.; Reeves, B. C.; Savović, J.; Berkman, N. D.; Viswanathan, M.; Henry, D.; Altman, D. G.; Ansari, M. T.; Boutron, I.; Carpenter, J. R.; Chan, A.-W.; Churchill, R.; Deeks, J. J.; Hróbjartsson, A.; Kirkham, J.; Jüni, P.; Loke, Y. K.; Pigott, T. D.; Ramsay, C. R.; Regidor, D.; Rothstein, H. R.; Sandhu, L.; Santaguida, P. L.; Schünemann, H. J.; Shea, B.; Shrier, I.; Tugwell, P.; Turner, L.; Valentine, J. C.; Waddington, H.; Waters, E.; Wells, G. A.; Whiting, P. F.; Higgins, J. P. ROBINS-I: A Tool for Assessing Risk of Bias in Non-Randomised Studies of Interventions. *BMJ* **2016**, i4919. https://doi.org/10.1136/bmj.i4919.
(15) Wells, G.; Shea, B.; O'Connell, J.; Robertson, J.; Peterson, V.; Welch, V. The NewcastleOttawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analysis.
(16) Shea, B. J.; Reeves, B. C.; Wells, G.; Thuku, M.; Hamel, C.; Moran, J.; Moher, D.; Tugwell, P.; Welch, V.; Kristjansson, E.; Henry, D. A. AMSTAR 2: A Critical Appraisal Tool for Systematic Reviews That Include Randomised or Non-Randomised Studies of Healthcare Interventions, or Both. *BMJ* **2017**, j4008. https://doi.org/10.1136/bmj.j4008.
(17) Centers for Disease Control and Prevention. *Diabetes.* https://www.cdc.gov/diabetes/index.html (accessed 2024-07-19).
(18) American Diabetes Association Professional Practice Committee; ElSayed, N. A.; Aleppo, G.; Bannuru, R. R.; Beverly, E. A.; Bruemmer, D.; Collins, B. S.; Cusi, K.; Darville, A.; Das, S. R.; Ekhlaspour, L.; Fleming, T. K.; Gaglia, J. L.; Galindo, R. J.; Gibbons, C. H.; Giurini, J. M.; Hassanein, M.; Hilliard, M. E.; Johnson, E. L.; Khunti, K.; Kosiborod, M. N.; Kushner, R. F.; Lingvay, I.; Matfin, G.; McCoy, R. G.; Murdock, L.; Napoli, N.; Perry, M. L.; Pilla, S. J.; Polsky, S.; Prahalad, P.; Pratley, R. E.; Segal, A. R.; Seley, J. J.; Selvin, E.; Silva, P. S.; Stanton, R. C.; Verduzco-Gutierrez, M.; Woodward, C. C.; Younossi, Z. M.; Gabbay, R. A. Introduction and Methodology: *Standards of Care in Diabetes—2024*. *Diabetes Care* **2024**, *47* (Supplement_1), S1–S4. https://doi.org/10.2337/dc24-SINT.
(19) American Dental Association. . https://engage.ada.org/.
(20) Covidence.
(21) Pedroso, J. de F.; Lotfollahi, Z.; Albattarni, G.; Arrruda Schulz, M.; Monteiro, A.; Sehnem, A. L.; Gidlund, M. A.; Figueiredo Neto, A. M.; Jardini, M. A. N. Influence of Periodontal Disease on Cardiovascular Markers in Diabetes Mellitus Patients. *Sci Rep* **2019**, *9* (1), 16138. https://doi.org/10.1038/s41598-019-52498-7.
(22) Mizutani, K.; Minami, I.; Mikami, R.; Kido, D.; Takeda, K.; Nakagawa, K.; Takemura, S.; Saito, N.; Kominato, H.; Sakaniwa, E.; Konuma, K.; Izumi, Y.; Ogawa, Y.; Iwata, T. Improvement of Periodontal Parameters Following Intensive Diabetes Care and Supragingival Dental Prophylaxis in Patients with Type 2 Diabetes: A Prospective Cohort Study. *Journal of clinical periodontology* **2024**, *51* (6), 733–741. https://doi.org/10.1111/jcpe.13958.
(23) Zhang, Y.; Leveille, S. G.; Camhi, S. M.; Shi, L. Association of Oral Care with Periodontitis and Glycemic Control among US Adults with Diabetes. *BMC Oral Health* **2023**, *23* (1), 903. https://doi.org/10.1186/s12903-023-03580-0.
(24) Enomoto, A.; Lee, A.-D.; Shimoide, T.; Takada, Y.; Kakiuchi, Y.; Tabuchi, T. Is Discontinuation of Dental Treatment Related to Exacerbation of Systemic Medical Diseases in Japan?. *British dental journal* **2023**. https://doi.org/10.1038/s41415-023-5690-3.

(25) Di Domenico, G. L.; Minoli, M.; Discepoli, N.; Ambrosi, A.; de Sanctis, M. Effectiveness of Periodontal Treatment to Improve Glycemic Control: An Umbrella Review. *Acta Diabetol* **2023**, *60* (1), 101–113. https://doi.org/10.1007/s00592-022-01991-z.
(26) Ata-Ali, F.; Melo, M.; Cobo, T.; Nagasawa, M. A.; Shibli, J. A.; Ata-Ali, J. Does Non-Surgical Periodontal Treatment Improve Glycemic Control? A Comprehensive Review of Meta-Analyses. *Journal of the International Academy of Periodontology* **2020**, *22* (4), 205–222.
(27) Lavigne, S. E.; Forrest, J. L. An Umbrella Review of Systematic Reviews Examining the Relationship between Type 2 Diabetes and Periodontitis: Position Paper from the Canadian Dental Hygienists Association. *Canadian journal of dental hygiene : CJDH = Journal canadien de l'hygiene dentaire : JCHD* **2021**, *55* (1), 57–67.
(28) Wu, S.-Y.; Wu, C.-Y.; Lin, L.-Y.; Chen, Y.-H.; Huang, H.-Y.; Lai, Y.-L.; Lee, S.-Y. Systemic Antibiotics Adjuvants to Scaling and Root Planing in Type 2 Diabetic and Periodontitis Individuals: Systematic Review with Network Meta-Analysis. *The Japanese dental science review* **2023**, *59*, 167–178. https://doi.org/10.1016/j.jdsr.2023.06.001.
(29) Esteves Lima, R. P.; Atanazio, A. R. S.; Costa, F. O.; Cunha, F. A.; Abreu, L. G. IMPACT OF NON-SURGICAL PERIODONTAL TREATMENT ON SERUM TNF-Alpha LEVELS IN INDIVIDUALS WITH TYPE 2 DIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS. *The journal of evidence-based dental practice* **2021**, *21* (2), 101546. https://doi.org/10.1016/j.jebdp.2021.101546.
(30) Obadan-Udoh, E.; Jordan, S.; Mudah, O.; Borgnakke, W.; Tavares, M. Gap Analysis of Older Adults With Type 2 Diabetes Receiving Nonsurgical Periodontal Therapy. *The journal of evidence-based dental practice* **2017**, *17* (4), 335–349. https://doi.org/10.1016/j.jebdp.2017.05.005.
(31) Simpson, T. C.; Clarkson, J. E.; Worthington, H. V.; MacDonald, L.; Weldon, J. C.; Needleman, I.; Iheozor-Ejiofor, Z.; Wild, S. H.; Qureshi, A.; Walker, A.; Patel, V. A.; Boyers, D.; Twigg, J. Treatment of Periodontitis for Glycaemic Control in People with Diabetes Mellitus. *Cochrane Database Syst Rev* **2022**, *4* (4), CD004714. https://doi.org/10.1002/14651858.CD004714.pub4.
(32) Elnour, M. A. A.; Mirghani, H. O. Periodontitis Treatment (Surgical and Nonsurgical) Effects on Glycemic Control: A Review and Meta-Analysis. *Ann Afr Med* **2023**, *22* (2), 131–135. https://doi.org/10.4103/aam.aam_53_22.
(33) Greggianin, B. F.; Marques, A. E. M.; Amato, A. A.; de Lima, C. L. Effect of Periodontal Therapy on Insulin Resistance in Adults with Dysglycemia and Periodontitis: A Systematic Review and Meta-Analysis. *Clinical oral investigations* **2023**, *27* (4), 1329–1342. https://doi.org/10.1007/s00784-023-04879-6.
(34) Pham, T. A. V.; Nguyen, P. A.; Tran, T. T. P.; Nguyen, V. T. T. Nonsurgical Periodontal Treatment Improved the Type 2 Diabetes Mellitus Status in Smokers: A Randomized Controlled Trial. *Diabetes research and clinical practice* **2022**, *194*, 110150. https://doi.org/10.1016/j.diabres.2022.110150.
(35) Kolte, R. A.; Kolte, A. P.; Bawankar, P. V.; Bajaj, V. A. Effect of Nonsurgical Periodontal Therapy on Metabolic Control and Systemic Inflammatory Markers in Patients of Type 2 Diabetes Mellitus with Stage III Periodontitis. *Contemporary clinical dentistry* **2023**, *14* (1), 45–51. https://doi.org/10.4103/ccd.ccd_514_21.
(36) Wang, Y.; Liu, H. N.; Zhen, Z.; Pelekos, G.; Wu, M. Z.; Chen, Y.; Tonetti, M.; Tse, H. F.; Yiu, K. H.; Jin, L. A Randomized Controlled Trial of the Effects of Non-Surgical Periodontal Therapy on Cardiac Function Assessed by Echocardiography in Type 2 Diabetic Patients. *J Clin Periodontol* **2020**, *47* (6), 726–736. https://doi.org/10.1111/jcpe.13291.

(37) Sundaram, S. G.; Ramakrishnan, T.; Krishnan, S. G.; Narayan, K. V.; Shankar, S.; Kanimozhi, G. Effect of Non-Surgical Periodontal Therapy on Systemic Inflammatory Markers, Glycemic Status and Levels of Proteinuria in Type 2 Diabetic and Non-Diabetic Patients With Chronic Periodontitis. *Cureus* **2023**, *15* (9), e44757. https://doi.org/10.7759/cureus.44757.
(38) Mammen, J.; Vadakkekuttical, R. J.; George, J. M.; Kaziyarakath, J. A.; Radhakrishnan, C. Effect of Non-Surgical Periodontal Therapy on Insulin Resistance in Patients with Type II Diabetes Mellitus and Chronic Periodontitis, as Assessed by C-Peptide and the Homeostasis Assessment Index. *J Investig Clin Dent* **2017**, *8* (3). https://doi.org/10.1111/jicd.12221.
(39) Bagde, H.; Sharma, A. K.; Chaubey, P. P.; Benjamin, N.; Ghosh, D.; Kaushal, L. Effect of Scaling and Root Planing in Conjunction with Antimicrobial Therapy on Glycated Hemoglobin Levels in Type 2 Diabetes Mellitus Patients. *Journal of pharmacy & bioallied sciences* **2023**, *15* (Suppl 2), S956–S959. https://doi.org/10.4103/jpbs.jpbs_268_23.
(40) Sato, M.; Ono, S.; Yamana, H.; Okada, A.; Ishimaru, M.; Ono, Y.; Iwasaki, M.; Aida, J.; Yasunaga, H. Effect of Periodontal Therapy on Glycaemic Control in Type 2 Diabetes. *Journal of clinical periodontology* **2024**, *51* (4), 380–389. https://doi.org/10.1111/jcpe.13939.
(41) Peng, C.-H.; Yang, Y.-S.; Chan, K.-C.; Kornelius, E.; Chiou, J.-Y.; Huang, C.-N. Periodontal Treatment and the Risks of Cardiovascular Disease in Patients with Type 2 Diabetes: A Retrospective Cohort Study. *Intern Med* **2017**, *56* (9), 1015–1021. https://doi.org/10.2169/internalmedicine.56.7322.
(42) Michalowicz, B. S.; Anderson, J. P.; Kottke, T. E.; Dehmer, S. P.; Worley, D. C.; Kane, S.; Basile, S.; Rindal, D. B. Periodontal Treatment and Subsequent Clinical Outcomes and Medical Care Costs: A Retrospective Cohort Study. *PloS one* **2023**, *18* (8), e0290028. https://doi.org/10.1371/journal.pone.0290028.
(43) Saito, M.; Shimazaki, Y.; Nonoyama, T.; Tadokoro, Y. Association between Dental Visits for Periodontal Treatment and Type 2 Diabetes Mellitus in an Elderly Japanese Cohort. *J Clin Periodontol* **2017**, *44* (11), 1133–1139. https://doi.org/10.1111/jcpe.12804.
(44) Milanesi, F. C.; Greggianin, B. F.; Dos Santos, G. O.; Toniazzo, M. P.; Weidlich, P.; Gerchman, F.; Oppermann, R. V. Effect of Periodontal Treatment on Glycated Haemoglobin and Metabolic Syndrome Parameters: A Randomized Clinical Trial. *Journal of clinical periodontology* **2023**, *50* (1), 11–21. https://doi.org/10.1111/jcpe.13717.
(45) Sanz, M.; Ceriello, A.; Buysschaert, M.; Chapple, I.; Demmer, R. T.; Graziani, F.; Herrera, D.; Jepsen, S.; Lione, L.; Madianos, P.; Mathur, M.; Montanya, E.; Shapira, L.; Tonetti, M.; Vegh, D. Scientific Evidence on the Links between Periodontal Diseases and Diabetes: Consensus Report and Guidelines of the Joint Workshop on Periodontal Diseases and Diabetes by the International Diabetes Federation and the European Federation of Periodontology. *Diabetes Res Clin Pract* **2018**, *137*, 231–241. https://doi.org/10.1016/j.diabres.2017.12.001.
(46) Ahern, J.; Nunn, J. The Integration of Oral Health-Related Best Practice Recommendations in the Management of Patients with Diabetes: A Cross-Sectional Survey of Primary Care Physicians. *J Public Health Dent* **2021**, *81* (3), 245–248. https://doi.org/10.1111/jphd.12397.
(47) Zhang, Y.; Qiao, D.; Chen, R.; Zhu, F.; Gong, J.; Yan, F. The Association between Periodontitis and Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. *Biomed Res Int* **2021**, *2021*, 6692420. https://doi.org/10.1155/2021/6692420.

(48) Anonymous. Evidence Review D for Periodontal Treatment to Improve Diabetic Control in Adults with Type 1 or Type 2 Diabetes: Periodontal Treatment to Improve Diabetic Control in Adults with Type 1 or Type 2 Diabetes: Evidence Review D. **2022**.
(49) Adda, G.; Aimetti, M.; Citterio, F.; Consoli, A.; Di Bartolo, P.; Landi, L.; Lione, L.; Luzi, L. Consensus Report of the Joint Workshop of the Italian Society of Diabetology, Italian Society of Periodontology and Implantology, Italian Association of Clinical Diabetologists (SID-SIdP-AMD). *Nutr Metab Cardiovasc Dis* **2021**, *31* (9), 2515–2525. https://doi.org/10.1016/j.numecd.2021.03.015.
(50) Herrera, D.; Sanz, M.; Shapira, L.; Brotons, C.; Chapple, I.; Frese, T.; Graziani, F.; Hobbs, F. D. R.; Huck, O.; Hummers, E.; Jepsen, S.; Kravtchenko, O.; Madianos, P.; Molina, A.; Ungan, M.; Vilaseca, J.; Windak, A.; Vinker, S. Periodontal Diseases and Cardiovascular Diseases, Diabetes, and Respiratory Diseases: Summary of the Consensus Report by the European Federation of Periodontology and WONCA Europe. *The European journal of general practice* **2024**, *30* (1), 2320120. https://doi.org/10.1080/13814788.2024.2320120.
(51) Tangpricha, V. *AACE Updated Comprehensive Type 2 Diabetes Management Algorithm with Endocrine Practice*; American Association for Clinical Endocrinology, 2023.
(52) American Diabetes Association Professional Practice Committee. 2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes—2022*. *Diabetes Care* **2022**, *45* (Supplement_1), S17–S38. https://doi.org/10.2337/dc22-S002.

Appendix A1

	Source:	*Ovid MEDLINE® ALL 1946 to June 04, 2024*	
		Searched 5 June 2024 by Karin Shank, NCBiotech	
		Strategy reviewed by Margaret Graton, NCBiotech	
	#	search string	# results
	1	*Diabetes Mellitus/ or exp *Diabetes Mellitus, Type 2/ or exp *Diabetes Mellitus, Type 1/	320515
	2	(diabetes mellitus or type 1 diabetes or type 2 diabetes).ti,ab. or diabetes.ti.	470925
	3	**1 or 2**	**542390**
Dental terms	4	exp *dental health services/ or *oral health/ or *preventive dentistry/ or exp *oral hygiene/ or exp *dental prophylaxis/ or exp *periodontics/ or *pulpitis/ or *candidiasis, oral/ or exp *stomatitis/ or exp *xerostomia/ or exp *periodontal diseases/ or exp *dental caries/ or exp *mouth, edentulous/	197420
	5	(dental or dentistry or periodont* or gingivitis or (gum adj3 disease*) or tooth loss or number of teeth or shortened dental arch or functional dentition or edentul* or missing teeth or missing tooth or prosthodonti* or ((dental or tooth or teeth or root or periapical) adj3 (cavit* or caries or carious or decay* or lesion*)) or oral health or oral disease* or DMF index or DMFT or DMFS).ti,ab.	408331
	6	(((endodontic or periapical or periodontal or gingival or tooth or teeth or mouth or oral or pulpal) adj3 (abscess* or infection*)) or pulpitis or oral candidiasis or stomatitis or xerostomia).ti,ab.	39435
	7	**4 or 5 or 6**	**508857**
	8	3 and 7	5767
	9	limit 8 to yr="2016 -Current"	2920
	10	9 and (Dental Care for Children/ or exp Pregnancy/ or Pregnant Women/ or exp Child/ or exp Infant/ or Adolescent/ or Diabetes, Gestational/)	244
	11	9 not 10	2676
	12	limit 11 to (address or autobiography or bibliography or biography or case reports or classical article or clinical trial, veterinary or comment or congress or dataset or dictionary or directory or duplicate publication or editorial or electronic supplementary materials or "expression of concern" or festschrift or historical article or interactive tutorial or interview or introductory journal article or lecture or legal case or legislation or letter or news or newspaper article or observational study, veterinary or periodical index or personal narrative or portrait or randomized controlled trial, veterinary or retracted publication or "retraction of publication" or technical report or video-audio media or webcast)	172
	13	11 not 12	2504

	14	limit 13 to animals	292
	15	13 and (exp in vitro techniques/ or exp drug evaluation, preclinical/ or exp models, animal/ or veterinary medicine/ or Clinical Trials, Veterinary as Topic/ or Observational Studies, Veterinary as Topic/ or exp animal experimentation/)	147
	16	13 and (animal model* or companion animal* or service animal* or disease model* or veterinar* or mouse or mice or rat or rats or rodent or rodents or swine or pig or pigs or rabbit or rabbits or murine or porcine or cat or cats or dog or dogs or feline or canine or monkey or monkeys or primate or primates or cow or cows or cattle or bovine or veterinar* or animal stud*).ti,ab.	317
	17	14 or 15 or 16	372
	18	**13 not 17**	**2132**

Appendix A2

List of excluded studies.

Study	PMID	Title	Reason for exclusion
Abduljabbar 2017	27686888	Role of lasers as an adjunct to scaling and root planing in patients with type 2 diabetes mellitus: a systematic review.	Wrong comparator
Al-Hamoudi 2017	28559203	Is antimicrobial photodynamic therapy an effective treatment for chronic periodontitis in diabetes mellitus and cigarette smokers: a systematic review and meta-analysis.	Wrong study design
Lira Junior 2017	28827017	Effects on HbA1c in diabetic patients of adjunctive use of systemic antibiotics in nonsurgical periodontal treatment: A systematic review.	Wrong comparator
Glurich 2019	31696343	Updates from the Evidence Base Examining Association between Periodontal Disease and Type 2 Diabetes Mellitus: Current Status and Clinical Relevance.	review
Corbella 2023	36849595	Laser treatments as an adjunct to non-surgical periodontal therapy in subjects with periodontitis and type 2 diabetes mellitus: a systematic review and meta-analysis.	Wrong intervention
Rapone 2022	36289786	Intensive Periodontal Treatment Does Not Affect the Lipid Profile and Endothelial Function of	Wrong outcomes

		Patients with Type 2 Diabetes: ARandomized Clinical Trial.	
Mirnic 2022	36140370	Effects of Nonsurgical Periodontal Therapy on Salivary 8-Hydroxy-Deoxyguanosine Levels and Glycemic Control in Diabetes Mellitus Type 2 Patients.	Wrong comparator
Pulivarthi 2022	35602530	Salivary tumor necrosis factor-alpha levels in periodontitis associated with diabetes mellitus after low level laser therapy as an adjunct to scaling and root planning: Arandomized clinical trial.	Wrong outcomes
Araujo 2022	35453306	Efficacy of Antioxidant Supplementation to Non-Surgical Periodontal Therapy on Metabolic Control in Type 2 Diabetes Patients: ANetwork Meta-Analysis.	Wrong intervention
Feng 2022	34610151	Adjunctive Er:YAG laser in non-surgical periodontal therapy of patients with inadequately controlled type 2 diabetes mellitus: A split-mouth randomized controlled study.	Wrong comparator
Sufaru 2022	35885519	The Effects of 810 nm Diode Laser and Indocyanine Green on Periodontal Parameters and HbA1c in Patients with Periodontitis and Type II Diabetes Mellitus: ARandomized Controlled Study.	Wrong study design

Borah 2022	35272460	Association Between Preventive Dental Care and Healthcare Cost for Enrollees With Diabetes or Coronary Artery Disease: 5-Year Experience.	Wrong setting
Luo 2022	34857389	Oral Health, Diabetes, and Inflammation: Effects of Oral Hygiene Behaviour.	Wrong intervention
Park 2022	35734903	Recovery from chronic periodontal disease is associated with lower risk for incident diabetes.	Wrong patient population
Dharmarajan 2022	36295619	The Effect of Laser Micro Grooved Platform Switched Implants and Abutments on Early Crestal Bone Levels and Peri-Implant Soft Tissues Post 1 Year Loading among Diabetic Patients-A Controlled Clinical Trial.	Wrong comparator
Kato 2023	36284054	Differences in periodontal parameters between SPT patients who regularly and irregularly visited the dental clinic analyzed at tooth level: a 14-year retrospective cohort study.	Wrong outcomes
Thakkar-Samtani 2023	36841690	Periodontal treatment associated with decreased diabetes mellitus-related treatment costs: An analysis of dental and medical claims data.	Wrong outcomes
SaracGul 2023	38055628	Melatonin supports nonsurgical periodontal treatment in patients with Type 2 diabetes mellitus	Wrong intervention

		and periodontitis: A randomized clinical trial.	
Shunmuga 2023	37749861	Clinical evaluation of the combined efficacy of injectable platelet-rich fibrin along with scaling and root planing in the non-surgical periodontal therapy of stage III and grade C periodontitis patients having type 2 diabetes mellitus: A randomized contr	Wrong outcomes
Hungund 2023	37312677	Efficacy of nonsurgical periodontal therapy affecting salivary biomarkers in non-diabetic and type 2 diabetic periodontitis patients. An observational study.	Wrong study design
Gd 2023	36751175	Effects of Non-surgical Periodontal Therapy on Saliva and Gingival Crevicular Fluid Levels of Chemerin in Periodontitis Subjects With and Without Type 2 Diabetes Mellitus.	Wrong intervention
Ghosh 2023	37854742	Effects of Scaling and Root Planing on Salivary Interleukine-6 Levels in Chronic Periodontitis Patients and Glycemic Controls.	Wrong patient population
Thankappan 2023	37781335	Emerging role of photodynamic therapy as an adjunct to nonsurgical periodontal therapy on periodontal status and glycemic control in patients with type 2 diabetes: Aclinical study.	Wrong study design

Guru 2023	35708712	Impact of scaling and root planing on salivary and serum plasminogen activator inhibitor-1 expression in patients with periodontitis with and without type 2 diabetes mellitus.	Wrong comparator
Rapone 2023	37170229	Research efficacy of gaseous ozone therapy as an adjuvant to periodontal treatment on oxidative stress mediators in patients with type 2 diabetes: a randomized clinical trial.	Wrong study design
Miller 2023	37042710	Biomarker panel discriminates diabetics with and without periodontitis pre- and post-therapy.	Wrong study design
Rahim 2023	37394484	Association and comparison of periodontal and oral hygiene status with serum HbA1c levels: a cross-sectional study.	Wrong study design
Huh 2023	37548156	Association of Dental Diseases and Oral Hygiene Care With the Risk of Heart Failure in Patients With Type 2 Diabetes: ANationwide Cohort Study.	Wrong outcomes
Syed 2023	37622627	Effects of Nonsurgical Periodontal Therapy on Glycemic Control in Diabetic Patients under Systemic Administration of Antidiabetic Ayurvedic Drug.	Wrong study design

Seniya 2023	37794537	Evaluation of salivary glycated albumin in periodontitis patients with and without type 2 diabetes mellitus and its changes with non-surgical periodontal therapy.	Wrong study design
Alblowi 2024	38533160	Comparative Study of Azithromycin Versus Doxycycline Effect on the Resistin Level in Periodontitis Patients With Type 2 Diabetes: A Randomized Controlled Clinical Trial.	Wrong outcomes
Xu 2024	38115631	Effects of amoxicillin and metronidazole as an adjunct to scaling and root planing on glycemic control in patients with periodontitis and type 2 diabetes: Ashort-term randomized controlled trial.	Wrong study design
Akansel 2024	38812655	Adjunctive use of laser biostimulation with nonsurgical periodontal therapy: a split-mouth, randomized, case-control study in diabetic and nondiabetic periodontitis patients.	Wrong study design
Cho 2020	32109666	Risk of peripheral arterial disease in patients with periodontitis: A nationwide, population-based, matched cohort study.	Wrong patient population
Tamashiro 2016	27013640	Amoxicillin Plus Metronidazole Therapy for Patients with Periodontitis and Type 2 Diabetes: A2-	Wrong outcomes

		year Randomized Controlled Trial.	
Nishihara 2017	29264035	Aperiodontal disease care program for patients with type 2 diabetes: A randomized controlled trial.	Wrong outcomes
Demirturk-Gocgun 2017	27855270	Role of Low-Level Laser Therapy as an Adjunct to Initial Periodontal Treatment in Type 2 Diabetic Patients: ASplit-Mouth, Randomized, Controlled Clinical Trial.	Wrong outcomes
Hayashi 2017	28431542	Effects of periodontal treatment on the medical status of patients with type 2 diabetes mellitus: a pilot study.	Wrong study design
Solowiej-Wedderburn 2017	28504365	Cost-effectiveness of non-surgical periodontal therapy for patients with type 2 diabetes in the UK.	Wrong setting
Agarwal 2017	22655911	Locally Delivered 0.5% Azithromycin as an Adjunct to Non-Surgical Treatment in Patients With Chronic Periodontitis With Type 2 Diabetes: A Randomized Controlled Clinical Trial.	Wrong study design
Jayakumar Sunandhakumari 2018	29899268	Effect of NonSurgical Periodontal Therapy on Plasma Levels of IL-17 in Chronic Periodontitis Patients with Well Controlled Type-II Diabetes Mellitus-A Clinical Study.	Wrong comparator

Barbosa 2018	29709606	Effect of photodynamic therapy as an adjuvant to non-surgical periodontal therapy: Periodontal and metabolic evaluation in patients with type 2 diabetes mellitus.	Wrong intervention
Duarte 2018	30076615	Clinical and microbiological effects of scaling and root planing, metronidazole and amoxicillin in the treatment of diabetic and non-diabetic subjects with periodontitis: Acohort study.	Wrong study design
Gao 2020	32773814	[Effect of initial periodontal therapy on blood parameters related to erythrocyte and platelet in patients with type 2 diabetes mellitus and chronic periodontitis].	Wrong study design
Choi 2020	31882408	Impact of Treating Oral Disease on Preventing Vascular Diseases: A Model-Based Cost-effectiveness Analysis of Periodontal Treatment Among Patients With Type 2 Diabetes.	Wrong setting
Perez-Losada 2016		Correlation between periodontal disease management and metabolic control of type 2 diabetes mellitus. A systematic literature review^ien	SysRev prior to 2020
Hasuike 2017		Systematic review and assessment of systematic reviews examining the effect of periodontal treatment on glycemic	SysRev prior to 2020

		control in patients with diabetes^ien	
MarÃaJosÃ© 2024		Nonsurgical Periodontal Care for Diabetes Patients: ACase-Control Study	Wrong study design
Matayoshi 2023		Effects of mouthwash on periodontal pathogens and glycemic control in patients with type 2 diabetes mellitus	Wrong intervention
Zhang 2023		Association Between Preventive Dental Visits and Flossing with Periodontitis and Diabetes Control â€“ National Health and Nutrition Examination Survey, 2011-2014	Wrong setting
Kiryowa 2021		Outcomes of Periodontal Treatment in Diabetes Mellitus Patients at Kiruddu Referral Hospital in Uganda. AProspective Cohort Study	Wrong patient population
Matayoshi 2024		Effects of mouthwash on periodontal pathogens and glycemic control in patients with type 2 diabetes mellitus.	Wrong intervention
Simpson 2022		Treatment of periodontitis for glycaemic control in people with diabetes mellitus.	already in a sysrev
Teshome 2016		The effect of periodontal therapy on glycemic control and fasting plasma glucose level in type 2 diabetic patients:	SysRev prior to 2020

		systematic review and meta-analysis.	
D'Aiuto 2018		Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial.	already in a sysrev
Lipman 2023		A Scoping Review of the Relation Between Toothbrushing and Diabetes Knowledge, Glycemic Control, and Oral Health Outcomes in People With Type 2 Diabetes.	Wrong intervention
Horbach 2021		Association between dental visits at primary care and glycated hemoglobin level in patients with type 2 diabetes: a cohort study	Wrong outcomes
Baeza 2020		Effect of periodontal treatment in patients with periodontitis and diabetes: systematic review and meta-analysis	SysRev prior to 2020
Velasco-Corredor 2018		Assessment of glycosylated hemoglobin (HbA1c) in type 2 diabetics before and after non-surgical periodontal treatment. A short-term follow-up study	Wrong outcomes
Wang 2017		Glycemic control and adipokines after periodontal therapy in patients with Type 2 diabetes and chronic periodontitis	already in a sysrev

Lucena 2017		Clinical and Metabolic Effects of two Periodontal Therapeutic Modalities in Diabetic Patients with Residual Pockets	Wrong intervention
Benrachadi 2019	30665791	The impact of periodontal therapy on the diabetes control: A systematic review	SysRev prior to 2020

Appendix A3

This is the list of studies included in this review either as a primary study, or included in the systematic reviews/review of reviews.

Study Name	Publication Year	Country	SR; Meta-analysis
Al-Zahrani	2009	Saudi Arabia	Wu 2023
Artese	2015	Brazil	Esteveslima 2021, Simpson 2022, Anonymous 2022
Auyeung	2012	Taiwan	Obadan-Udoh 2017
Babladi	2018	India	Greggianin 2023
Bagde	2023	India	Primary Study
Bazyar	2018	Iran	Esteveslima 2021
Bharti	2013	Japan	Esteveslima 2021, Obadan-Udoh 2017
Botero	2016	Colombia	Lavigne 2021
Bukleta	2018	Kosovo	Simpson 2022, Anonymous 2022, Di Domenico 2022
Calbacho	2004	Chile	Simpson 2022, Anonymous 2022
Chandra	2019	India	Di Domenico 2022
Chen	2012	China	Esteveslima 2021, Obadan-Udoh 2017, Simpson 2022, Wu 2023, Anonymous 2022, Di Domenico 2022
Choi	2020	USA	Primary Study
Cirano	2012	Brazil	Obadan-Udoh 2017
Corbella	2013	Italy	Lavigne 2021
Correa	2010	Brazil	Esteveslima 2021
D'Aiuto	2018	UK	Simpson 2022, Anonymous 2022
Dag	2010	Turkey	Esteveslima 2021
Das	2019	India	Elnour 2023, Simpson 2022, Wu 2023, Anonymous 2022
Dengizek	2019	Turkey	Di Domenico 2022
D'Aiuto	2018	UK	Elnour 2023
El-Makaky	2020	Egypt	Simpson 2022, Wu 2023, Anonymous 2022
Engebretson	2011	USA	Di Domenico 2022
Engebretson	2013	USA	Elnour 2023, Greggianin 2023, Obadan-Udoh 2017, Simpson 2022, Anonymous 2022, Di Domenico 2022
Engebretson & Kocher	2013	USA/Germany	Ata-Ali 2020
Enomoto	2023	Japan	Primary Study
Faggion	2016	Germany	Lavigne 2021

Faria-Almeida	2006	Spain	Obadan-Udoh 2017
Felipe	2015	Brazil	Simpson 2022, Anonymous 2022
Gaikwad	2013	NA	Di Domenico 2022
Gay	2014	USA	Elnour 2023, Simpson 2022, Anonymous 2022, Di Domenico 2022
Geisinger	2016	USA	Esteveslima 2021, Wu 2023
Gilowski	2012	NA	Di Domenico 2022
Gilowski	2012	Poland	Obadan-Udoh 2017
Hasuike	2017	Japan	Lavigne 2021
Hayashi	2017	Japan	Esteveslima 2021
Iwamoto	2001	Japan	Esteveslima 2021, Greggianin 2023
Jain	2019	India	Ata-Ali 2020, Lavigne 2021
Janket	2005	USA	Ata-Ali 2020
Javid 2019a	2019	Iran	Esteveslima 2021
Javid 2019b	2019	Iran	Esteveslima 2021
Jones	2007	USA	Obadan-Udoh 2017, Simpson 2022, Anonymous 2022
Kanduluru	2014	NA	Di Domenico 2022
Kapellas	2017	Australia	Elnour 2023, Simpson 2022, Anonymous 2022
Kara	2015	Turkey	Esteveslima 2021
Kardesler	2010	Turkey	Esteveslima 2021
Katagiri	2009	Japan	Simpson 2022, Anonymous 2022
Katagiri	2012	Japan	Esteveslima 2021
Kaur	2015	India	Simpson 2022, Wu 2023, Anonymous 2022, Di Domenico 2022
Kaur	2015	UK	Elnour 2023
Khader	2010	Jordan	Obadan-Udoh 2017
Kiran	2005	Turkey	Simpson 2022, Wu 2023, Anonymous 2022, Di Domenico 2022
Kolte	2023	India	Primary Study
Koromantzos	2011	Greece	Elnour 2023, Obadan-Udoh 2017, Simpson 2022, Anonymous 2022, Di Domenico 2022
Koromantzos	2012	Greece	Obadan-Udoh 2017
Kothiwale	2013	India	Simpson 2022, Anonymous 2022
Kumar	2015	India	Esteveslima 2021

Lee	2020	Korea	Simpson 2022, Anonymous 2022
Li	2011	China	Obadan-Udoh 2017, Simpson 2022, Anonymous 2022
Li	2015	China	Ata-Ali 2020, Lavigne 2021
Liew	2013	Australia	Ata-Ali 2020
Lin	2012	Taiwan	Obadan-Udoh 2017
Lopez	2014	Chile	Obadan-Udoh 2017
Mammen	2017	India	Greggianin 2023, Primary Study
Matsumoto	2009	Japan	Obadan-Udoh 2017
Mauri-Obradors	2018	Spain	Simpson 2022, Anonymous 2022
Michalowicz	2023	USA	Primary Study
Milanesi	2023	Brazil	Primary Study
Miranda	2014	Brazil	Wu 2023, Di Domenico 2022
Mizuno	2017	Japan	Simpson 2022, Wu 2023, Anonymous 2022, Di Domenico 2022
Mizutani	2024	Japan	Primary Study
Moeintaghavi	2012	Iran	Elnour 2023, Simpson 2022, Wu 2023, Anonymous 2022, Di Domenico 2022
Navarro-Sanchez	2007	Spain	Obadan-Udoh 2017
Nishioka	2019	Japan	Greggianin 2023
O'Connell	2008	NA	Di Domenico 2022
Pedroso	2019	Brazil	Primary Study
Peng	2017	Taiwan	Primary Study
Pham	2022	Vietnam	Primary Study
Promsudthi	2005	Thailand	Obadan-Udoh 2017
Qureshi	2021	Pakistan	Simpson 2022, Wu 2023, Anonymous 2022
Raman	2014	Malaysia	Obadan-Udoh 2017, Simpson 2022, Anonymous 2022, Di Domenico 2022
Rapone	2021	Albania	Simpson 2022, Anonymous 2022
Rocha	2001	Mexico	Obadan-Udoh 2017
Rodrigues	2003	Brazil	Wu 2023, Di Domenico 2022
Rodrigues	2015	Brazil	Simpson 2022, Anonymous 2022
Saengtipbovorn	2014	Thailand	Obadan-Udoh 2017
Saito	2017	Japan	Primary Study

Sato	2024	Japan	Primary Study
Sgolastra	2013	Italy	Ata-Ali 2020, Lavigne 2021
Simpson	2010	UK	Ata-Ali 2020
Simpson	2015	UK	Ata-Ali 2020, Lavigne 2021
Singh	2008	India	Simpson 2022, Wu 2023, Anonymous 2022, Di Domenico 2022
Srirangaraja n	2016	India	Greggianin 2023
Stewart	2001	NA	Di Domenico 2022
Stewart	2001	USA	Obadan-Udoh 2017
Sun	2010	China	Obadan-Udoh 2017
Sun	2011	China	Elnour 2023, Simpson 2022, Anonymous 2022
Sun	2014	China	Ata-Ali 2020
Sundaram	2023	India	Primary Study
Talbert	2006	USA	Esteveslima 2021
Tasdemir	2016	Turkey	Esteveslima 2021, Greggianin 2023
Teeuw	2010	Netherlands	Ata-Ali 2020
Telgi	2013	India	Simpson 2022, Anonymous 2022, Di Domenico 2022
Tsalikis	2014	Greece	Obadan-Udoh 2017, Wu 2023, Di Domenico 2022
Tsobgny-Tsague	2018	Cameroon	Simpson 2022, Wu 2023, Anonymous 2022, Di Domenico 2022
Vergnes	2018	France	Elnour 2023, Simpson 2022, Anonymous 2022
Wang	2014	China	Ata-Ali 2020
Wang	2020	China	Primary Study
Wang S	2017	China	Elnour 2023, Esteveslima 2021, Simpson 2022, Wu 2023, Anonymous 2022, Di Domenico 2022
Wang Y	2017	Hong Kong	Simpson 2022, Anonymous 2022
Wu	2015	China	Wu 2023, Di Domenico 2022
Yun	2007	China	Simpson 2022, Anonymous 2022
Zhang	2013	China	Obadan-Udoh 2017, Simpson 2022, Anonymous 2022, Di Domenico 2022
Zhang	2023	USA	Primary Study

Appendix A4

Amstar2 ratings of the systematic reviews and review of reviews:

Author, Year	1[a]	2[b]	3[c]	4[d]	5[e]	6[f]	7[g]	8[h]	9[i]	10[j]	11[k]	12[l]	13[m]	14[n]	15[o]	16[p]	non-critical domains	Critical domains (blue colums)	Overall
Elnour 2023	YES	NO	YES	YES	YES	YES	NO	YES	YES	NO	YES	NO	YES	YES	NO	YES	2	3	critically low
Greggianin 2023	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	NO	NO	YES	NO	YES	2	2	low
Esteves Lima 2021	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	NO	NO	YES	NO	YES	2	2	low
Simpson 2022	YES	YES	YES	YES	YES	YES	yes	YES	YES	yes	YES	yes	yes	YES	yes	YES	0	0	high
Wu 2023	YES	YES	YES	YES	YES	YES	NO	YES	YES	NO	YES	YES	YES	YES	YES	YES	1	1	low
DiDomenico 2023	YES	YES	YES	YES	YES	YES	yes	YES	YES	NO	YES	YES	YES	YES	YES	YES	1	0	high
Fadi 2020	YES	YES	YES	YES	YES	YES	yes	YES	YES	yes	YES	YES	YES	YES	yes	YES	0	0	high
Lavigne 2021	YES	YES	YES	YES	YES	YES	yes	YES	YES	yes	YES	YES	YES	YES	NO	YES	0	1	Low
Obadan-Udoh 2017	YES	NO	YES	YES	YES	YES	NO	YES	yes	yes	NA	NA	NO	YES	NO	NO			critically low

Risk of bias assessments of primary studies:

ROB of randomized clinical trials:	Risk of Bias Domains					Overall Risk of bias	Mapping to quality terms used in this report
Author Year	D1	D2	D3	D4	D5		
Pham 2022	Low	Low	Low	Low	Low	Low	High
Milanesi 2023	Low	Low	Low	Low	Low	Low	High
Kolte 2023	Low	Low	Low	Low	Low	Low	High
Wang 2020	Low	Low	Low	Low	Low	Low	High

Sundaram 2023	Some concerns	Some concerns	Low	Low	Low	Some concerns	Moderate

	ROBINS risk of bias for non-controlled studies: Risk of Bias Domains								
Author Year	D1	D2	D3	D4	D5	D6	D7	Overall risk of bias	Mapping to Quality terms used in report
Pedroso2019	Low	Low	Low	Low	Low	Low	Low	Low	High
Mizutani 2024	Low	Serious	Low	Serious	Moderate	Moderate	Low	Serious	Low

Newcastle-Ottawa Score for cohort studies	Selection				Comparability	Outcome				
Author Year	Representativeness of Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Outcome of Interest Not Present at Study Start	Comparability of Cohorts	Assessment of Outcome	Follow-up Long Enough for Outcome	Adequacy of Follow-up of Cohorts	Quality	Mapping to Quality terms used in report
Mammen 2017	1	1	1	1	1	0	1	1	Good	High
Bagde 2023	1	1	1	1	0	0	1	1	Poor	Low
Sato 2024	1	1	1	1	1	1	1	1	Good	High
Peng 2017	1	1	1	1	1	1	1	1	Good	High
Michalowicz 2023	1	1	1	1	1	1	1	0	Good	High
Saito 2017	1	1	1	1	1	1	1	0	Good	High
Zhang 2023	1	1	0	0	1	1	0	1	Fair	Moderate
Enomoto 2023	1	1	0	0	0	0	0	0	Poor	Low